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FAVIPIRAVIR

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Description of the drug

Favipiravir is an antiviral drug produced by the Fujifilm Toyama Chemical Co. Ltd and approved by the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan in 2014, under the trade name of Avigan, for the treatment of influenza from new or re-emerging viral strains that do not respond to conventional antiviral therapies [1]. The drug has been used off-label in other countries to treat several infections, including Ebola and Lassa, and on February 15th it was approved in China for the treatment of SARS-CoV-2 infection. The use of the medicine is not authorized in European Union countries neither in the USA.

Rationale for off label use of the drug for the treatment of SARS-CoV-2 infections

The rationale for the use of favipiravir in the treatment of COVID-19 is based on the experience of a Chinese research team that carried out an open-label, controlled and non-randomized clinical trial at the Third People's Hospital of Shenzhen (China) on 80 new coronavirus-positive patients. From preliminary study results, favipiravir showed a higher antiviral activity than lopinavir/ritonavir, in terms of virus elimination and rate of improvement of the thoracic CT image [2]. However, as authors highlighted, the results must be interpreted with caution considering the preliminary nature of the study, which has methodological limitations (open-label study, no randomization, in both groups patients took interferon alfa-1b).

Pharmacodynamic characteristics and mechanism of action

Favipiravir is a new type of RNA-dependent RNA polymerase inhibitor (RdRp), analogue of purine nucleic acid, which exerts its antiviral activity through its active metabolite, favipiravir-RTP (favipiravir ribofuranosyl-5 '-triphosphate) [3]. The active metabolite is recognized as a substrate that selectively and powerfully inhibits RNA-dependent RNA polymerase (RdRp) of RNA viruses, thus preventing replication of the viral genome. Since the catalytic domain of RdRp is preserved in various types of RNA viruses, this mechanism of action supports a wider spectrum of antiviral activities of favipiravir [4]. Some studies have also found that the presence of purine analogues may reduce the antiviral

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activity of favipiravir, suggesting competition between favipiravir-RTP and purine nucleosides for RdRp binding [5]. Favipiravir, therefore, is active against a wide range of flu viruses, including A (H1N1) pdm09, A (H5N1) and the avian virus A (H7N9). It also inhibits flu strains resistant to current antiviral drugs and shows a synergistic effect in combination with oseltamivir. Several in vitro and animal studies have shown that favipiravir blocks the replication of many other RNA viruses, including arenaviruses [6], flebovirus, hantavirus [7], flavivirus [8], enterovirus, alphavirus, western equine encephalitis virus [9], norovirus [10], paramyxovirus, and respiratory syncytial virus [11].

Pharmacokinetic characteristics

The pharmacokinetics of favipiravir is complex, time and dose dependent and can be influenced by body weight [12]. Bioavailability is almost complete at 97.6%. The average Cmax is 51.5 µg/mL. The drug has an apparent volume of distribution of 15-20 L and a 54% drug-protein binding, mainly to serum albumin. Favipiravir is extensively metabolized through hydroxylation from aldehyde oxidase. Favipiravir metabolites are mainly eliminated via kidneys. The elimination half-life of favipiravir is estimated between 2 and 5.5 hours. In addition, lower than expected plasma levels have been observed in patients with Ebola virus infection or with severe flu symptoms, raising concerns about the alteration of bioavailability and / or metabolism in seriously ill patients [13, 14].

Treatment scheme in COVID-19 patients

The oral dose regimen of favipiravir approved for the treatment of adult patients with new or re-emerging flu virus infection involves two administrations of 1600 mg on the first day and two daily administrations of one 600 mg dose in the following days. Treatment should not exceed 5 days. Data from some clinical studies reported different dosage regimens. Indeed, during the study NCT01728753 the drug was administered in two daily doses of 1800 mg on the first day and 800 mg on the following days (from day 2 to day 5) [15]. In the studies NCT02008344 and NCT02026349, two international phase 3 randomized and placebo controlled clinical trials. The drug was administered in two administrations of a loading dose of 1800 mg on day 1 and two daily administrations at a dose of 800 mg for the following four days (2-5 days) [16, 17]. In the study on the efficacy of favipiravir in the treatment of COVID-19 patients, a dosing regimen of two daily doses of 1600 mg was adopted on the first day of therapy, followed by two daily doses of 600 mg from the second day for a duration of 14 days in addition to IFN-a1b 60 mg two days per aerosol [2].

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Interactions

If multiple drugs are administered, different drug-drug interactions could occur. In particular, in healthy volunteers the co-administration of paracetamol and favipiravir resulted in significant increases of approximately 20% of the total exposure to paracetamol. Concomitant treatment with theophylline resulted in an approximate 30% increase in favipiravir Cmax levels; other precautions for use include the co-administration of pyrazinamide, repaglinide, and famciclovir [15].

Drug Toxicity Monitoring

Based on single dose toxicity studies, the lethal dose for oral and intravenous favipiravir in mice is estimated to be> 2000 mg / kg. In rats, the lethal dose for oral administration is> 2000 mg / kg, while the lethal dose in dogs and monkeys is> 1000 mg / kg. The symptoms of overdose seem to include body weight reduction, vomiting and reduced locomotor activity. Favipinavir has shown a good safety profile in more than 2,000 healthy volunteers enrolled in phase I clinical trials and in patients enrolled in phase II or III clinical trials for the treatment of influenza [18]. The adverse reactions that occurred were mainly dose-dependent, including asymptomatic increases in plasma uric acid levels, diarrhea, asymptomatic increases in liver enzymes, and neutropenia [12]. No Grade 3 or 4 ADRs emerged in clinical trials that evaluated the effects of favipinavir in the treatment for Ebola [19]. However, it was not possible to draw clear conclusions on the efficacy of favipinavir and on its teratogenicity [20]. Due to the risk of teratogenicity and embryotoxicity that emerged from preclinical studies, the drug is contraindicated in pregnant women and breast-feeding women. On October 2018, the PMDA communicated changes in precautions of use for favipiravir due to a risk of abnormal behavior. This risk, which was reported in patients with influenza, can lead to accidental falls. Although there is no clear correlation between abnormal behavior and antiviral medication, all precautions should be used during treatment.

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