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FAVIPIRAVIR: A PRIMARY TREATMENT OF COVID-19

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ABSTRACT

Favipiravir generally comes under antiviral activity. Favipiravir shows pharmacokinetic and pharmacodynamic activity. The mechanism depends on RNA dependent. And it was effective against different viruses. Favipiravir is available in different combinations such as Hydro chloroquinoline, Oseltamivir, Theophylline, Raloxifene, Hydralazine, etc. The article grants a comparative duty of issued logical assessments either as separate drug or in combinations so that it is supportive for research professors worldwide. Favipiravir use in the treatment of not only COVID-19 but also in Nipah, Ebola, Influenza and other kinds of virus treatment also.

The author here mentions drug interaction and dose level with also cover different parameters. Dose of favipiravir may cause a problem in uric acid. And also, wish to present more data of favipiravir due to current COVID-19 Situation.

KEYWORDS: Favipiravir, COVID-19, Influenza, Nipah, Ebola.

INTRODUCTION

Favipiravir has been official to treat influenza in Japan and discovered by Toyama Chemical Co., Ltd. Phenotypic showing against influenza virus at Research Laboratories. It is first specified for novel influenza (strains that cause more severe disease) as a substitute for seasonal influenza. And also, its advanced clinical development in the US.[1,2] It being studied for the treatment of Nipah virus, Ebola virus and coronavirus disease 2019 (COVID-19). And nowadays in coronavirus disease more used.[3] It's important to find effective treatment options as the disease progresses and have a potential impact on global health. In addition to other drugs used to treat the disease (such as lopinavir, ritonavir, ribavirin and chloroquine phosphate), the use of favipiravir is also used in many clinical trials. Favipiravir is similarly to nucleic purine acid and viral RNA dependent RNA polymerase (RdRp) inhibitor. The Bureau of Pharmaceuticals and Medical Devices of Japan in 2014 for the treatment of influenza virus infection was permitted as an antiviral drug. It is also studying the treatment of several other viral infections, including COVID-19.[4] Favipiravir (T-705) has tested strong antiviral activity against many RNA virus families and is now in clinical estimation for the treatment of influenza.[5] Favipiravir retailed under the name of Avigan, Avifavir, FabiFlu, Favipira and Areplivir. And its IUPAC name is 6-fluoro-3-hydroxy-2-pyrazine carboxamide is an energetic antiviral prodrug. Favipiravir originally also called T-705. The additional pyrazine carboxamide derivative as antiviral drugs T-1105 and T-1106, having the structural formula, as shown in Figure 1.[6,7] It is a purine nucleic acid analogue that inhibits the RNA-dependent RNA polymerase enzyme and is approved in Japan for the treatment of influenza.

The metabolite favipiravir furanofuranosyl 5′-triphosphate. It inhibits virus replication by preventing RNA Polymerase 20. Although most of the preclinical safety and effectiveness data of favipiravir comes from studies that have proved that it has antiviral activity against the Ebola virus and influenza virus, and it has also shown efficacy Resistance to SARS-CoV-2 infection. A new in vitro study directed by Wang et al. showed that in Vero E6 in cells when the effective concentration of favipiravir is 61.88μM/L, it actually has an effect on SARS-CoV-2. These ones the results of preclinical and in vitro studies provide an optimistic basis for the prospects of Favipiravir in the treatment of COVID-19. It is based on urgent and compassionate use in many countries. Finally, this research advocating more evidence needs to assess long-term due to the limited available data on safety issues that have not yet been resolved, effective treatment effects cannot be obtained. After that, Physicians must be very careful and vigilant when using favipiravir for COVID-19.[7]

PHARMACOKINETICS

Absorption

Favipiravir is run as a prodrug. It's superb bioavailability (~94%), 54% protein binding, and a coffee volume of distribution (10- 20 L). It reaches Cmax within two hours after one dose. Not only Tmax but also half-life increase after multiple doses. Favipiravir features a short half-life (2.5- 5 h), resulting in rapid renal elimination within the hydroxylated form.[8]

Metabolism

Favipiravir may be a prodrug that metabolizes by ribosylation and phosphorylation, forming a lively form referred to as the favipiravir-ribofuranosyl-5′-triphosphate, (favipiravir-RTP). Its metabolites by elimination of renal excretion. Favipiravir is generally metabolized by aldehyde oxidase (AO) and moderately to a hydroxylated form by xanthine oxidase (XO). In revisions using human liver microsomes, formation of the hydroxylate ranged from 3.98 to 47.6 pmol/mg protein/min, through an inter-individual difference of AO activity by 12 times at extreme. A glucuronate conjugation was observed in human plasma and urine as a metabolite aside from the hydroxylated form.

It's not metabolized by the cytochrome P450 system but inhibits one among its components (CYP2C8). Thus, it must be used with caution when co-administered with drugs metabolized by the CYP2C8 system.[8]

Excretion

Favipiravir was mainly excreted as a hydroxylated form into the urine, and a tiny amount of unchanged drug was observed. In an oral 7-day multiple-dose study with six healthy adults, the cumulative urinary excretion ratio of the unhanged drug and therefore the hydroxylated form was 0.8% and 53.1%, respectively, during 48 hours after the last administration.[8]

Elimination is refereed by aldehyde oxidase as well as marginally by xanthine oxidase. Favipiravir exhibits neither dose-dependent nor time-dependent pharmacokinetics.[8]

PHARMACODYNAMICS

It is measured that favipiravir is processed in cells to a ribosyl triphosphate form (Favipiravir RTP) which favipiravir RTP selectivity inhibits RNA polymerase involved in influenza viral replication. Favipiravir RTP (1000 µmol/L) showed no inhibitory effect on α, 9.1-13.5% inhibitory effect on β and 11.7-41.2% inhibitory effect on ϒ by regards to the action against human DNA polymerase α, β and ϒ. Favipiravir RTP on human RNA polymerase II was 905 µmol/L by the inhibitory concentration (IC_{50}).

MECHANISM OF ACTION

Favipiravir drive over an intracellular phosphoribosylation to be a dynamic form, favipiravir-RTP (favipiravir ribofuranosyl-5β-triphosphate), which is documented as a substrate by RdRp and prevents the RNA polymerase action. Since the catalytic domain of RdRp is conserved among various kinds of RNA viruses, therefore it preventing viral transcription and replication.[1] This mechanism of action supports a broader spectrum of antiviral activities of favipiravir. Favipiravir is actual in contradiction of a good range of types as well as subtypes of influenza viruses, with strains immune to existing anti-influenza drugs.[1,9]

Including favipiravir-RTP into the recently formed RNA strand can prevent it from extending and spreading the viral genome. favipiravir-RTP and purine nucleosides competitively bind to RNA-dependent RNA polymerase, which ultimately affects virus replication and transcription.[10]

The mechanism of its actions is expected to be related to the selective inhibition of viral RNA-dependent RNA polymerase. Favipiravir might be a prodrug that's absorbed to its dynamic form, favipiravir-ribofuranosyl-5'-triphosphate (favipiravir-RTP), obtainable in both oral and also intravenous formulations. And its indications in Figure 2. Favipiravir-RTP may be a nucleoside analogue. It copies both guanosine as well as adenosine used for the viral RdRp.[11]

It has currently been exposed that favipiravir encourages lethal mutagenesis in vitro during influenza viral infection, making it a virucidal drug. Whether an identical activity is confirmed against SARS-CoV-2 or not is uncertain. [8,11]

COMBINATION OF DRUGS WITH FAVIPIRAVIR

Combination of drug available in the local market together with favipiravir or co-administered drug-like Hydro chloroquinoline, Oseltamivir, Theophylline, Raloxifene, Hydralazine, etc. Hydro-chloroquinoline: Both favipiravir and HCQ are recommended for mild, moderate, and severe patients diagnosed or suspected with COVID-19. We realized a central database for data assembly. Demo-graphic features like age, gender, symptoms and onset time, comorbidities, medications, physical examination, fever, and vital signs were recorded. Laboratory tests like complete blood count, blood qualitative analysis (including renal and liver function), coagulation parameters, acute phase reactants (ferritin, C-reactive protein (CRP), procalcitonin (PCT) were obtained. Both X-ray and computerized tomography (CT) of the chest were used for radiological assessment. last, consistent with results obtained during this single centre retrospective observational study on laboratory established mild to moderate COVID-19 adult patients, not only HCQ but

also HCQ plus favipiravir treatments are connected to reduced risk of ICU admission related with the action regimen of favipiravir alone.[12]

Oseltamivir: Both Favipiravir and oseltamivir are antiviral compounds used for the dealing of influenza infections. We've pointed to research the efficacy of the compounds composed to treat influenza H1N1 virus infections in mice. Lung virus titers were reduced by treatment with favipiravir alone or with favipiravir collective with oseltamivir, relative to placebo treatment. The combination resulted in additional decreases in lung virus titers compared with favipiravir monotherapy. Favipiravir and Oseltamivir are regularly mutual. Oseltamivir may be a cyclohexene carboxylate ester. It's an antiviral prodrug being hydrolyzed to the active free acid within the liver. Oseltamivir is employed to slow the spread of influenza. It's a task as a prodrug.[13] Combination therapy with the help of antiviral agents may reduce the incidence of drug resistance emergence. Treatment with a drug combination like favipiravir plus oseltamivir should be more beneficial than treatment with oseltamivir alone. Mixtures of favipiravir and oseltamivir were effective against these two H_1N_1 virus infections, with no adverse effects related to through the treatments of the mice. Groupings of oseltamivir and favipiravir were synergistically actual in falling mortality in animals diseased with the H275Y virus.[14]

Treatment of Favipiravir on Various Disease:

COVID-19: There's a partial indication signifying that associated with additional antiviral drugs, favipiravir might improve outcomes for people with COVID-19, but more difficult studies are required before any conclusions are repeatedly drawn. As of September 2020, several clinical trials of favipiravir as a treatment for COVID-19 had been managed or were ongoing.[6,15] Drug fever is trying to diagnose in patients with febrile illnesses, especially if the drug may be a novel drug for an emerging communicable disease like COVID-19.

Ebola: Research in 2014 recommended that favipiravir may have usefulness against Ebola supported educations in mouse models; effectiveness in humans stayed unaddressed. During the Ebola virus in West Africa in 2014, a French nurse contracted Ebola while volunteering for Doctors Without Borders (MSF) in Liberia and apparently recovered after taking a course of favipiravir. In December 2014, a clinical trial examined the use of favipiravir for Ebola virus disease, Guinea. Preliminary results published at the Conference on Retroviruses and Opportunistic Infections (CROI) in 2016 (provided in advance) showed that low-dose and low-dose patients had reduced mortality-the level of virus in the blood is moderate, but for patients with high levels (Patients at higher risk of death) had no effect. The filovirus can cause diseases with a high fatality rate and is a cautious biohazard factor. [16] The experimental plan was parallel criticized for by means of only historical controls.[6] Favipiravir remains a broad-spectrum antiviral agent that consumes confirmed efficacy in contradiction of Ebola virus (EBOV) in rodents. Favipiravir and metabolite 1 (M1) levels remained evaluated in treated NHPs. [17,18]

Nipah: The name 'Nipah' originates from a Malaysian village, somewhere the first outbreak was started in 1998-1999.[19] Nipah and Hendra viruses are newly emerged bat-borne paramyxoviruses (genus *Henipavirus*) triggering severe encephalitis and respiratory illness in persons with fatality rates oscillating from 40–75%.[20]

Nipah virus stands as a connective mediator of occurrences of encephalitis with pneumonia and has a high circumstance fatality rate. The first outbreak happened in Malaysia-Singapore, connected to contact with pigs in slaughterhouses and an outbreak in the Philippines linked to the killing of horses; greatest outbreaks have valuable India and Bangladesh. in Bangladesh, outbreaks are often related to ingesting raw date palm liquid contaminated by saliva and urine of fruit bats. Popular knowledge delivered in the Scientific Reports, Syrian hamster model for Nipah virus infection was castoff, which carefully mirrors most features of human diseases, such as extensive vasculitis, pneumonia, and encephalitis. The hamsters continued diseased with a dose of 10^4 PFU NiV-M via the intraperitoneal (i.p.) route like previous studies, and treatment was initiated immediately after infection. Favipiravir stayed succeeded double every day through the peroral (p.o.) route for 14 days. The preserved hamsters showed 100% existence and no clear morbidity after lethal NiV challenge, while all the regulator belongings expired of simple disease.[6] Human to human transmission and nosocomial infections were a protuberant feature in this outbreak.[19]

Favipiravir consumes well-known use against a broad spectrum of RNA viruses through adherents of the *Paramyxoviridae*, *Filoviridae*, *Arenaviridae families*, and the *Bunyavirales* order. We nowadays determine that favipiravir has forceful antiviral activity in contradiction of henipaviruses. *In vitro*, favipiravir reserved Nipah and Hendra virus copying and transcript at micromolar attentions. [20] However, cases with slight and general features were recognized. Fever, headache, dizziness, myalgia, vomiting and loose stools have been familiar as non-specific prodromal symptoms in many outbreaks of Nipah.[19]

Influenza: Favipiravir inhibits 53 kinds of influenza viruses with seasonal strains A (H_1N_1), A (H_3N_2), and influenza B; the A (H_1N_1), pandemic virus(PDM); highly infective avian influenza virus A (H5N1) isolated from humans; A (H_1N_1) and A (H_1N_2)

secluded from swine; and A (H_2N_2), A (H_4N_2), and A (H_7N_2). it's also active against drug-resistant strains of the virus, including M2 and NA inhibitors.[8,10]

Other: In researches in animals, favipiravir consumes exposed action in contradiction of West Nile virus, yellow jack virus, hoof-and-mouth disease virus similarly as other flaviviruses, arenaviruses, bunyaviruses and also alphaviruses. Action against enteroviruses and valley fever virus consumption likewise remained established. Favipiravir has shown partial efficiency against the Zika virus in animal studies but was less effective than other antivirals like MK-608. The agent has also exposed to efficacy against rabies and has been used empirically in approximate humans infected with the virus.[6, 8]

DRUG INTERACTIONS:

Pyrazinamide: Affiliated routine of pyrazinamide with favipiravir growths the quantity of acid. Regular acid level nursing is obligatory when these drugs are used together. When pyrazinamide 1.5g once daily and favipiravir 1200mg /400mg BID remained administered, the blood acid level stayed 11.6 mg/dL. After pyrazinamide was directed alone, and 13.9 mg/dL together with favipiravir.[8]

Repaglinide: Favipiravir constrains the breakdown of repaglinide finished the CYP2C8 pathway, therefore growing its probable to reason toxicity (hypoglycemia, headache, increase incidence of upper tract infections, etc.).[21,22] Thoughtfully connected usage is recommended.[8,21]

Theophylline: Theophylline increases the blood levels of favipiravir, and opposing responses to favipiravir might occur. Famciclovir, sulindac: Efficiency of individuals drugs might too be reduced after co-administered by favipiravir.[8,23]

Acyclovir: Acyclovir may postponement the change of favipiravir into the energetic mediety, therefore dipping the condition antiviral efficacy.[8]

In clinical trials for antiviral purposes, the dosing regimen is critical.

The IC_{50} of favipiravir differs from nanomolar to micromolar concentrations counting on viral studies. So, dosage necessities and routines might similarly be dissimilar between behaviours. The authorized favipiravir treatment used for influenza in Japan contains a 3,200 mg oral loading dose (1,600 mg every 12 hours) scheduled day 1, followed by 600 mg twice daily scheduled days 2–5. Higher treatment (1,800 mg twice daily on day one followed by 800 mg twice daily thereafter) is furthermore accepted in phase III clinical trial. The safety and effectiveness of this method of treating influenza have long been established.[9,24,25]

The adverse outcome of favipiravir might be clinically significant in affected role with a past of gout, hyperuricemia, kidney function damage (in which blood concentration of M1 increases), and somewhere there's an affiliated custom of additional drugs disturbing blood acid elevation.[26,27]

The main adverse reactions are mild to moderate diarrhoea, an asymptomatic increase of blood acid and transaminases, and a decrease within the neutrophil counts. [28,29] Also in shock, anaphylaxis, pneumonia, Acute kidney injury and Colitis haemorrhagic.[9,24, 30]

FAVIPIRAVIR INCREASES URIC ACID LEVEL

Favipiravir is absorbed to an inactive metabolite M1 by aldehyde oxidase and xanthine oxidase and expelled into the urine.[31] Inside the kidney, acid treatment is controlled by the balance of reabsorption and tubular secretion within the proximal tubules. Favipiravir, as well as M_1 performance as rational inhibitors of organic anion transporter one and three (OAT1 and OAT3), which remain complicated in acid defecation inside the kidney. Additionally, M1 enhances acid reuptake via urate transporter 1 (URAT1) within the proximal renal tubules.[8] Therefore, favipiravir is supposed toward decreases acid excretion into urine, leading to elevation of acid levels in the blood. Raised acid levels remained refunded to normal after the termination of favipiravir, and favipiravir isn't used for extended periods of your time for the treatment of virus infection. Thus, the effect on blood acid levels was subclinical in most studies.[18, 33]

Uric acid may be a product of the metabolic breakdown of purine nucleotides. Hyperuricemia, which is an abnormally high acid level within the blood, can cause gout and is related to other medical conditions, including kidney function impairment. This review summarizes the mechanism for blood acid elevation caused by favipiravir. [21,26, 34] Favipiravir undergoes metabolism within the liver mainly by aldehyde oxidase and partially by xanthine oxidase, producing an inactive metabolite favipiravir-M1 excreted by the kidneys. Favipiravir is extensively metabolized, with just one recovered unchanged in the urine. Cytochrome P450 isoenzymes don't contribute to the metabolism of favipiravir.[35,36] Favipiravir can increase blood acid levels. In phase I-II safety studies, the effect was observed in a dose-dependent manner.[26, 37]

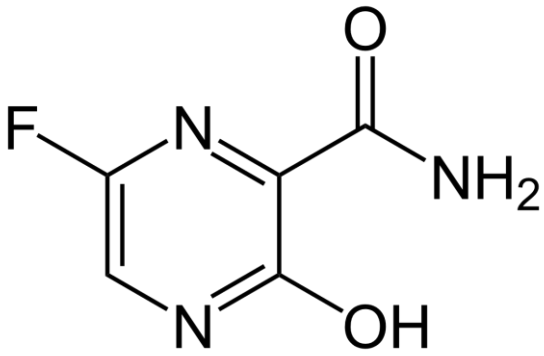

Figure1: Structure of Favipiravir.

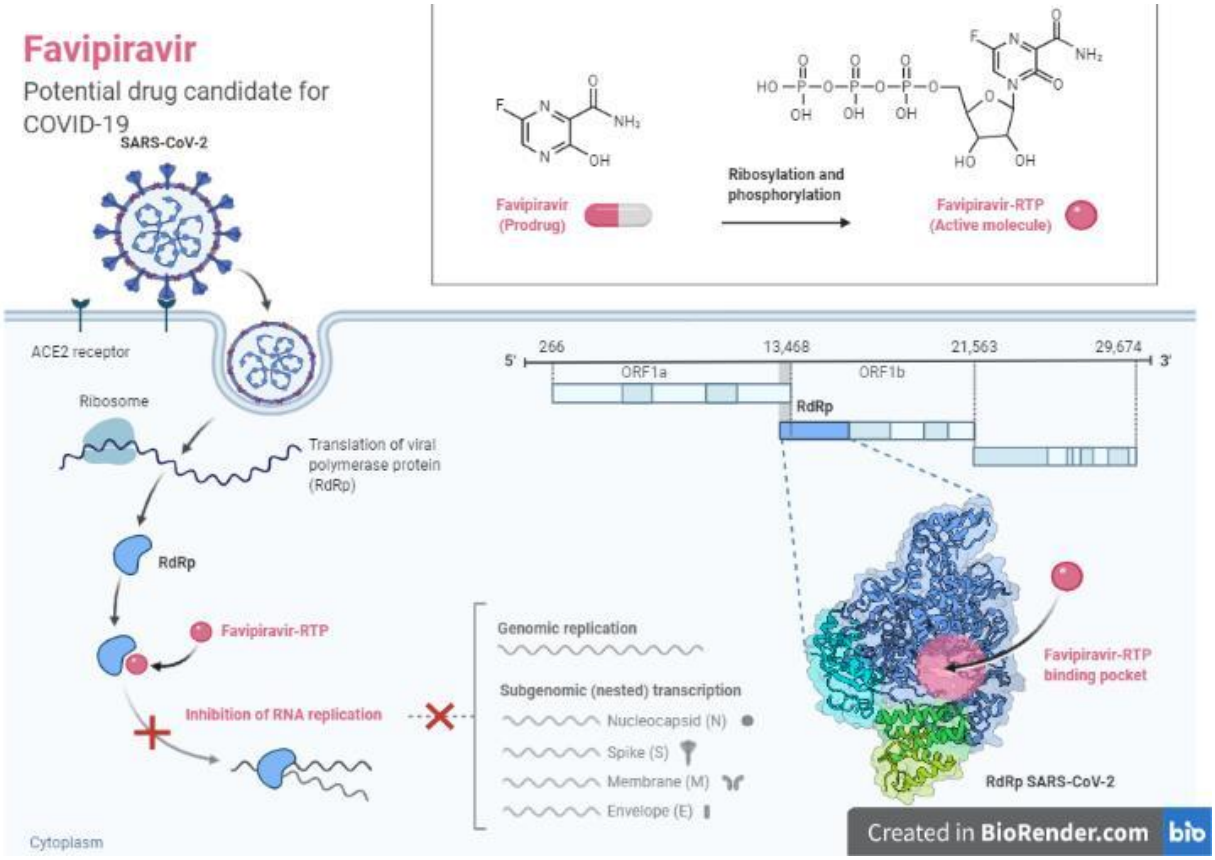

Figure 2: Favipiravir mechanism of action.

CONCLUSION

Compared with Covid-19, Favipiravir may be essential to ensure effective treatment, reduce mortality and discharge early. The general state drawn from the current analysis and other educations on the treatment of COVID-19 on favipiravir seems to be a relatively safe drug. Because SARS-CoV-2 is a new virus, researchers around the world are still deciphering the virus, and the pattern of human biochemical and pathological changes brought about by SARS-CoV-2.

Favipiravir is useful in several kinds of Influenza viruses, irrespective of sensitivity or unaffected to remaining anti-influenza drugs. Favipiravir, a drug which has a similar mechanism of action to remdesivir nonetheless is orally administered, takings less strong supportive data to back its custom, but is yet developing as a representative that is value considering in mild to moderate cases.

In addition, most of the safety data of favipiravir come from research on people infected with the Ebola virus and influenza virus. Because the interaction between drugs and diseases may be different, the drug-related ADE may be different in different diseases. These key facts must be careful when estimating the safety of favipiravir against COVID-19 in additional clinical studies. The current analysis describes the snapshot based on limited data on the use of favipiravir in COVID-19. More extensive evidence is needed to assess the long-term and rare adverse effects of favipiravir. In conclusion, "The SARS-CoV-2 contagion stunned the

world, and the only way to fight it is to study additional around it."

Though, additional clinical studies are immediately needed to assess the usefulness and protection of this antiviral nucleoside in the treatment of COVID-19.

CONFLICT OF INTEREST

All the authors declare that they have no conflict of interest.

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