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Review Article

DETAILED INFORMATION ON FAVIPIRAVIR: DRUG FOR TREATMENT OF SARS-COV-2

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ABSTRACT

Severe acute respiratory syndrome corona virus-2 (SARS-CoV-2) is another name given to pandemic disease COVID-19 that is caused by a newly discovered coronavirus. People infected with coronavirus will experience mild-to-moderate respiratory illness, and it can be seen in a serious stage when comorbidities include along with it. This is now creating a huge pandemic situation all over the world with a huge rate of sufferers, that is, around 9.06 million around the world and about 440 k in India till today according to the World Health Organization. This is a serious condition that should be solved with vaccine only as coronavirus is undergoing mutation it makes difficult to invent a vaccine for it. So far, about 200 genetic mutations have been discovered across the world also in these 198 mutations appeared independently more than once. Due to this pandemic situation, there are so many clinical trials going on in discovering vaccines. Recently, after many trails conducting favipiravir are found to be the most successful in treating any stage of SARS-CoV-2. This article focuses completely on this area, along with its mechanism, side effects, uses, and contraindications.

Keywords: SARS-CoV-2, Favipiravir, Future hopes.

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INTRODUCTION

Severe acute respiratory syndrome corona virus-2 (SARS-CoV-2) is caused by a coronavirus. The structure consists of spikes which are a type of protein that is most essential in causing infection to human cells. Furthermore, spikes now are undergoing tremendous changes in a structure known as mutations that change the entire function and properties of the virus and lead to the production of new strain about 14 strains due to mutations in spikes. Beta-coronavirus has three major classes that made zoonosis diseases that include SARS-CoV-2 that occurred in 2002, infected 8000 people, and killed 800 next again after 10 years in 2012 MERS-CoV caused a highly lethal effect about 35% mortality rate now another class SARS-CoV-2 emerged with heavy loss to human health all over the world and also caused huge loss economically [1]. The novel coronavirus is showing a high rate of mutations; still, there are any researches going on to discover more strains. Due to the pandemic and the situations, the World Health Organization has declared the situation as Public Health Emergency of International Concern [2].

Commonly, all viruses mutate, but speed rate is important in discovering vaccines. Most virus mutations do not change viral protein referred to as silent mutations, while other mutations change the amino acid sequence of viral protein. Even change in sequence does not affect functionally, so these are called inert also some mutations make viruses functionally different making a lineage of a virus [3] Fig. 1 [4].

INFLUENCE OF STRAINS IN VACCINE

When different strains are evolving, it becomes difficult to invent vaccines as the vaccine provides long-term protection. Normally dose, DNA, and MVA-vaccines encode S glycoprotein neutralizes antibodies also N protein (induce long-lived memory T cells) in the case of MERS and SARS. So now, this aspect became a potentially viable alternative long term T-cell immunity against in coronavirus [5].

The strain that is inert will preserve the features that will provide immunity against a whole group of variants which make it easier to study and make a perfect unique target in discovering vaccines against it [6]. As there are more mutations in SARS-CoV-2, an RNA vaccine can be more powerful than involves supplementing a similar section of the genome in the form of RNA into the host body [7].

It became a challenge for scientists all over the world to discover vaccines with no side effects after performing many experiments in different phases and by a comparative study between many drugs they have discovered favipiravir is the most effective drug in treating SARS- CoV-2 [8]. Other drugs work in treating the condition of SARS-CoV-2 such as dexamethasone, lopinavir/ritonavir, ivermectin, and remdesivir [9].

PHASES IN DEVELOPMENT OF VACCINE

When they find a new vaccine towards any disease, they need to undergo the following process before getting that vaccine into the market:

- Pre-clinical tests: This includes the primary stage first done *in vitro* (test tube or cell culture) and also *in vivo* (animals). This process helps testing preliminary efficacy, toxicity, pharmacokinetics, and safety information of vaccines. When this stage passes, then they can try for the next step on human [10].
- Phase – 1: In this phase, they conduct rails in 20–80 humans for several months watching regularly. This phase has a significance in tracing out the highest dose, side effects, and the best route of administration [11].
- Phase – 2: Here, experiments will be done on 25–100 people that they categorize them into different groups and compare the studies between them and intervein the results.
- Phase – 3: In this site, the study size is increased to 3000 participants and this is the last phase of clinical trials and when this passes that they give the approval to release the drug into the market [12].
- Approval: After phase-3 trials, the candidate who performs the experiments applies for approval of his vaccine to release it into the market. However, when there occurs a pandemic situation that vaccines can be approved under emergency authorization [13].

FAVIPIRAVIR IN SARS-COV-2

The Drug Controller General of India has approved favipiravir as emergency medical use on June 19, in India. Favipiravir is the first oral approved medicine in India for treating SARS-CoV-2 launched by Glenmark Pharmaceuticals with the name FabiFlu for conducting Phase 3 clinical trials in patients with mild-to-moderate symptoms [8]. Hence, it is important to know about side effects mechanism and details about favipiravir.

STRUCTURE

Favipiravir is a new RNA polymerase inhibitor that is previously used in treating influenza-A and B. It also works as an antiviral ebolavirus, sand virus, bunia virus, and rabies virus [14]. The chemical structure is known as T-705; 6-fluoro-3-hydroxy-2-pyrazine carboxamide (pyrazine carboxamide derivative). This undergoes intracellular phosphoribosylation to form an active substance that is favipiravir ribofuranosyl-5'-triphosphate (favipiravir-RTP) [14], as shown in Fig. 2 [15].

MECHANISM

The active form, that is, favipiravir RTP interacts with RNA dependent RNA polymerase to inhibit replication of viral genome in host cells. Furthermore, from another hypothesis, it is thought to be that the active form can be incorporated into the nascent RNA strand and prevents its elongation and viral proliferation an transcription [16].

DOSAGE

Dosage includes 200 mg*9 tabs on 1st day followed by 200 mg*4 tablets for next 14 days [17].

From the preliminary report by Japan, it is clear that when they performed an observational study they found that about 73.8% of mild, 66.6% of moderate, and 40.1% of the severe condition of SARS-CoV-2 had improved their condition after 7 days start of favipiravir; improved outcome after 14 days for mild cases is 87.8%, for moderate cases is 84.5%, for severe cases is 60.3% also more than 50% of patients with a mild infection, 42.7% with moderate, and 14.7% with severe infection had discharged alive from hospital [18].

PHARMACOKINETICS

According to studies from japan on protein binding capacity in human serum albumin is about 65% and to α_1-acid glycoprotein is 6.5% it is found that the maximum plasma concentration of favipiravir is 2 h from oral administration while the half-life is 2–5.5 h [19].

Absorption

The bioavailability is about 97.6% and the Cmax is 51.5 μg/mL. Favipiravir has many interactions with 200 types of food items that decrease Cmax so to compensate tis the dose needs to be increased [16]. Drug-drug interactions can lead to serious conditions, especially in patients with comorbidities and complications such as hypertension, diabetes, and cardiovascular disease [19].

Distribution

As favipiravir is a prodrug and its activation occurs in the liver; also, the volume of distribution will be different between prodrug (favipiravir) and active metabolite (favipiravir-RTP). There are still ongoing experiments at the clinical trial stage [20]. However, for favipiravir, the volume of distribution is 15–20 mL [21].

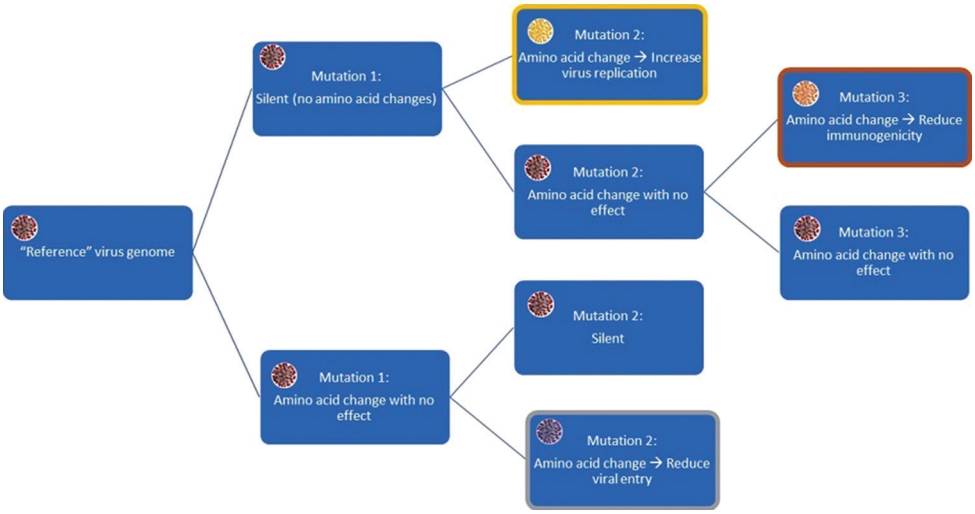

Fig. 1:

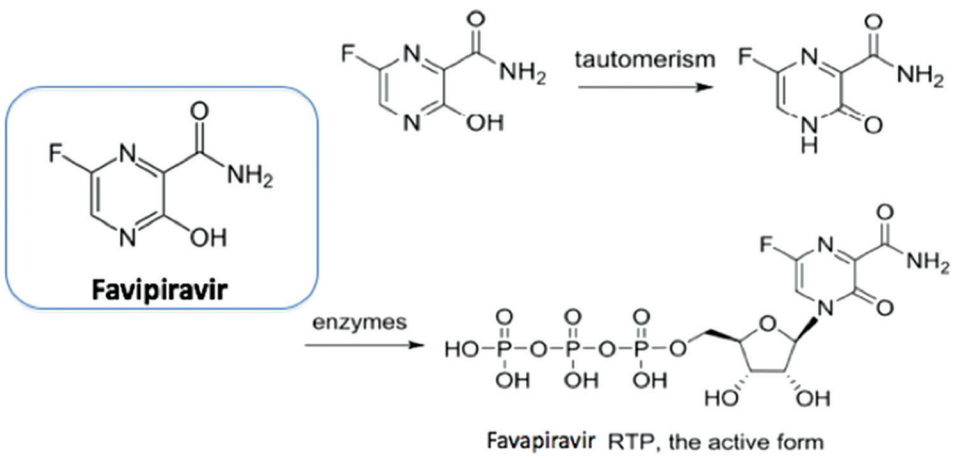

Fig. 2: Intracellular phosphoribosylation [15]

Metabolism
Normally, all the antivirals undergo hydroxylation primarily by aldehyde oxidase and also by xanthine (minimum effect) [22]. From studies, it is found that human liver microsomes are sites for hydroxylation that forms favipiravir hydroxylate at a range of 3.98–47.6 pmol/mg protein/min. The range may vary with the average of aldehyde oxidase activity by 12 times to maximum [23]. Along with hydroxylating, glucuronate conjugate is also observed in human plasma [24].

Excretion
It is excreted through urine in hydroxylate form also a little amount of unchanged drug in the ratio of 53.1%:0.8%, respectively [23].

Toxicity
There is no information about toxicity levels in humans, while in another family, there is information as follows: Lethal dose for oral and intravenous in mice is estimated more than 2000 mg/kg, the lethal dose for oral administration in rats is >2000 mg/kg, and lethal dose for dog and monkeys is >1000 mg/kg [21].

Symptoms of overdose
Reduced body weight, vomiting, and decreased locomotor activity. While when it comes to dogs, rats, and monkeys with oral administration that include decreased red blood cells; increased liver function parameters such as AST, ALP, ALT, and bilirubin; increased vacuolation in hepatocytes; also, testis toxicity is also observed [22].

Pregnancy and lactation
Favipiravir is teratogenic, so it is contraindicated in pregnancy and also in breastfeeding women, it is contraindicated as it is excreted in breast milk [25].

Dosage adjustments

Hepatic impairment

When favipiravir toxicity occurs, it still worsens the situation in liver functioning. Hence, the doe should be maintained.

Renal impairment

As it is excreted through urine in different forms, it should be monitored in patients with renal failure. However, the dosage is still under clinical trials [23].

Use in pediatrics

The efficacy and safety of children are not found yet [23].

Adverse drug reactions

Increased blood uric acid, hypersensitivity reactions, and a little effect on the respiratory system, blurred eye vision, and vertigo.

Monitoring parameters in patients with:

Shock, anaphylaxis, pneumonia, hepatitis, jaundice, acute kidney disease, decreased WBC, neurological and psychiatric symptoms, colitis hemorrhage [23].

List of contraindicated drugs:

There is a big list of drugs that interact with favipiravr and has an effect on pharmacokinetics and pharmacodynamics. The list can be checked here (drug bank) [21].

DISCOVERY

Favipiravir has been used as an anti-influenza virus that ranged from 0.013 to 0.48 μg/ml for influenza A virus, from 0.039 to 0.089 μg/ml for influenza B virus, and 0.030 to 0.057 μg/ml for influenza C virus. The mammalian cell lines like Madin-Darby Canine Kidney Cells (MDCK cells), Vero cells there is no toxicity shown up to 1000 μg/ml. MDCK cells are inoculated with seasonal influenza viruses and seen for the lethal effects.

The cell data are shown in Table 1.

The clinical research method includes the assay with XXT. XXT is first converted to aqueous formazan by an enzyme in cells, in which we are looking for testing. The compounds are then diluted to the concentration like the volume of 100 μl with test medium in 96 well-cultured plates that contain a concentration of 2×10^3cells/100 μL. The test plate is incubated for 3 days at 37°C in 100% humidity and 5% CO_2. After 3 days, 50 μl of XXT reagent that contains 1 mg/ml in FCS free EMEM containing 5 Mm phenazine methosulfate is added, and the reaction product is assayed [26].

RECENT UPDATES ON FAVIPIRAVIR IN SARS-COV-2 TREATMENT

There are many clinical trials going on in different countries all over the world and different stages. The list is as follows:

- From clinical study to evaluate, the performance and safety of favipiravir in COVID-19 that has been conducting from March 2020. It is randomized, double-blind and placebo-controlled (1:1), the screening process is done from 10 days after the onset of COVID-19. Here, there is given favipiravir with 1800 mg BID on 1st day and 600 mg TID for the next 14 days and the other groups were given with placebo with the same dose. These groups are made a comparative study to evaluate the efficacy of favipiravir in 100 subjects. In this, I subject has any renal impairment that the dose has decreased to 600 mg BID even then if adverse reactions continue then the subject is discontinued from treatment. Still, the trail is in Phase 3 in Italy, for the outcome of clinical recovery for the time frame of 90 days [27].
- From a multi-center, randomized, double-blind, and placebo-controlled, Phase 3 study evaluating favipiravir for treatment of COVID-19 started from May 2020 for the outcome of recovery with a time frame of 28 days with favipiravir or placebo administration to normalize the conditions such as respiratory rate, SPO_2, and relief from cough. With the administration of favipiravir combined with supportive care with a dose of 1800 mg*2 for day-1 and with 600 mg*3 for the next 14 days and other with placebo according to current national/local guidelines. This is going on in China, Germany, and Romania [28].
- Another study of the use of favipiravir in hospitalized subjects with COVID-19 conducting in the United States starting from April 2020 to determine the effect of favipiravir plus standard of care (SOC) with that of the only SOC on viral clearance of COVID-19 as measured by nasopharyngeal and oropharyngeal sampling for the time frame of 29 days. The interventional study is in Phase 2 by administering 1800

Table 1:

Cell lines	Assay type	Incubation time	Activity description
MDCK cells	Function assay		Inhibition of viral replication of influenza A virus (A/Hong Kong/213/03 [H5N1]) and influenza A virus (A/Ann Arbor/6/60 [H2N2]) hybrid virus in MDCK cells by neutral red uptake assay
Vero cells	Function assay	7–8 days	Antiviral activity against Junin virus Candid-1 in Vero cells assessed as inhibition of virus-induced visual cytopathic effect after 7–8 days
MDCK cells	Function assay		Inhibition of influenza A virus (A/duck/Minnesota/1525/1981 [H5N1]) replication in MDCK cells by neutral red uptake assay

mg BID favipiravir plus SOC or SOC alone on day-1 then 1000mg BID favipiravir plus SOC or SOC alone for the next 13 days, but if the subject is suffering from any liver impairment dose was decreased to 800 mg BID. The study is done for 14 days treatment follow-up for the next 46 days in about 50 patients in three different sites of the US for the outcome [29].

- The completed clinical trial on the study of safety and efficacy of favipiravir in management of COVID-19 started in April and completed on June 1 2020 in about 100 subjects for the outcome of viral clearance at 14 days' time frame by conducting PCR analysis test at 48–72 h apart and also clinical improvement at 14 days' time frame by administering favipiravir at 3200 mg (1600 mg 12 hourly) on day-1 then 1200 mg (600 mg 12 hourly daily) for 10 days and in another group for comparison by administering oseltamivir 75 mg 12 hourly for 5–10 days and hydroxychloroquine 400 mg 12 hourly day1 followed by 200 mg 12 hourly for day 2-day10 and comparison was done between these groups done in Egypt [30].
- By study on oral favipiravir compared to placebo in subjects with mild COVID-19 going from April 2020 in Phase 2 randomized, double-blinded, and placebo-controlled study of oral favipiravir comparing with the SOC in subjects with mild or asymptomatic COVID-19 by administering SOC plus favipiravir for 10 days and evaluated for 28 days and in another group SOCplus placebo that is equal to favipiravir for 10 days and evaluated for 28 days for the study done by US [31].

Many clinical trials are going on, but few are listed above others can be seen on the clinicaltrails.gov website.

Even there are some conditions, where favipiravir is used in treating the condition of pneumonia progression and cytokine increase and also to improve the condition of respiratory function and produce immediate relief from critical or severe conditions even [32].

Future health care, a pharma company has announced to launch favipiravir drug under the brand name XARAVIR to treat mild and moderate COVID-19 cases [33].

COMBINATION THERAPY

With methylprednisolone

When favipiravir, along with methylprednisolone, was administered in patients with a severe condition of COVID-19 and they are on the ventilator as they have SPO2 <93% which have been recovered well and even they do not require ventilator further but the administration should be started in early-stage only to achieve favorable outcomes [34].

With umifenovir

Glenmark has approved that an antiviral combination can effectively be used in high viral loads in the early stage of the disease such as umifenovir that has that the combined effect has a comprehensive antiviral cover on the pre-entry and post-entry life cycle of SARS-CoV-2. The combination has shown its effectiveness in clinical trials, and further studies are carrying on [35].

CONCLUSION

For SARS-CoV-2, there are still many drugs that are being discovered that are in several stages of trails, but favipiravir is the first oral drug that is launched by Glenmark. There are still trails going on for combination therapy with favipiravir, hoping for good results to discover them. This article gives detailed information about favipiravir.

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