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THE EVOLUTION OF ANTIVIRAL AGENT MOLNUPIRAVIR FOR TREATMENT AND PROPHYLAXIS OF COVID-19 IN PANDEMIC- REVIEW ARTICLE

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ABSTRACT COVID-19 is currently well known among the general population. The current pandemic treatment requires patient compliant, safe, tolerable, and orally effective. RNA dependent RNA polymerase (RdRp) is an important enzyme involved in RNA synthesis by the formation of phosphodiester bonds within the virus. Effective oral antiviral agents are urgently needed to treat, block transmission and prevent progression to severe illness in COVID-19. Molnupiravir is a orally active RdRp inhibitor. The Developmental steps of molnupiravir includes prophylactic efficacy in a ferret model and its therapeutic efficacy against COVID-19 patients has been proven.

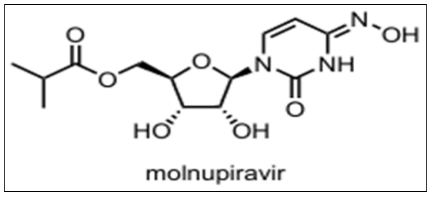
KEYWORDS : EIDD-2801, EIDD-1931, RdRp inhibitor, Remdesivir

Introduction:

COVID-19 pandemic is a public Health Emergency where effective drug necessary for treatment and prevention of severe acute respiratory syndrome coronavirus-2 (SARS CoV-2). In older patients, immunocompromised individuals and with comorbidity includes hypertension, diabetes, malignancies, cardiovascular diseases or chronic lung diseases are increased risk of fatality. RdRP in-hibitor drugs are potent enough for drug repurposing against COVID-19 infection. Broad-spectrum class of viral RdRp inhibitors are the analogue of nucleoside or nucleotide, including Remdesivir, Molnupiravir, Favipiravir, Galidesivir, Ribavirin, Sofosbuvir, and Tenofovir[1]. In December 2021, FDA granted an emergency use authorization (EUA) to molnupiravir due to uncertainty for COVID-19 patients. Molnupiravir was originally developed for the treatment of influenza at Emory University, USA[2]. This drug has also demonstrated activity against a variety of viruses, including SARS CoV-2. The objective of this review article is to enlighten the researchers working on COVID-19 about the mechanism, discovery, recent developments related to molnupiravir.

Structure of Molnupiravir:

Molnupiravir is a pyrimidine ribonucleoside analog with a chemical name of (2R,3S,4R,5R)-3,4-dihydroxy-5-(4-hydroxyamino)-2-oxopyrimidine (2H) tetrahydrofuran-2-yl) methyl isobutyrate. The other names of molnupiravir are EIDD-1931-isopropyl ester, EIDD-2801, MK-4482, uridine and β-D-N4-hydroxycytidine

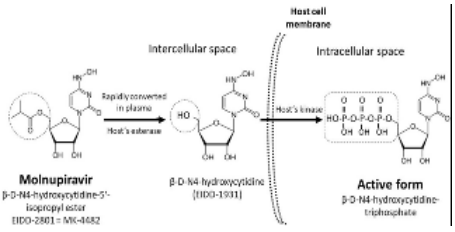


β-D-N^4-hydroxycytidine[3].(fig.1)

Fig.1: Structure of Molnupiravir

Mechanism of action of Molnupiravir:

Molnupiravir (EIDD-2801) is effective against RNA viruses by inhibiting RNA dependent RNA polymerase which induce RNA mutagenesis. Molnupiravir, (EIDD-2801) β-D-N4-hydroxycytidine 5-isopropyl ester is a prodrug of β-D-N4-hydroxycytidine (EIDD-1931). It is rapidly converted into EIDD-1931 in the plasma by the host's esterase. In host cells, EIDD-1931 is intracellularly transformed into its active form, β-D-N4-hydroxycytidine-triphosphate, which inhibits viral replication through its incorporation into the viral genome. Repeated accumulation of mutations results in the viral error catastrophe[4] (Fig.2).



Drug development steps of Molnupiravir against Covid-19:

Phase 0 clinical trial:

Human lung tissues of LoM was inoculated with SARS-CoV-2 and determined the virus replication titre after exposure at 2,6 and 14th days, titres were highest after two days of infection. It was widely distributed throughout the tissues, majority of cells were positive for viral RNA. Further evaluation of SARS-CoV-2 infection in human lung tissue affects predominantly ciliated airway cells and type II pneumocytes due to type I interferon and inflammatory responses. Evaluated the therapeutic use of EIDD-2801 to inhibit SARS-CoV-2 replication in vivo in LoM, using a dose that is similar to the human dose in clinical trials. EIDD-2801 tested the efficacy of pre-exposure prophylaxis and also effectively reduced the number of infectious particles in the human lung tissue of LoM after infection. Hence it is used for both prophylactic and therapeutic administration against SARS-CoV-2 replication[5].

Phase I clinical trial:

Randomized, double blind, placebo controlled study was conducted in healthy human subjects. Pharmacokinetic property, effect of food on pharmacokinetics, safety, and tolerability were evaluated for single and multiple doses of molnupiravir. It absorbed well in plasma with concentration range of 50–1600 mg with median time of 1.00–1.75 h in a dose-dependent manner. Reported adverse effects were mild (93%)[1].

Phase II clinical trial:

Optimal dose and safety of molnupiravir were evaluated in SARS CoV-2 patients with mild symptomatic infection. 18 SARS CoV-2 infected patients were enrolled, oral doses of 300, 600 and 800 mg of molnupiravir given BID for five days or a placebo. Primary outcome was higher dose limiting toxicity and secondary outcomes were safety,

virological response, pharmacokinetics and clinical progression. All three doses of molnupiravir was well tolerated without any serious adverse effects[6].

Phase III clinical trial:

Double blind and randomized study conducted in non hospitalised and hospitalised adult COVID-19 patients for safety and efficacy of molnupiravir. On interim analysis, risk of hospitalization or death was significantly decreased up to 50% and drug induced adverse events were same in both groups among non hospitalised patients. Clinical benefits of molnupiravir in hospitalized patients were not significant[1]. Medicine regulatory authority of UK has authorized the antiviral drug mulnopiravir to manage mild to moderate COVID-19 infection in non hospitalised adult patients with one risk factor for severe disease.

Comparing efficacy with other approved RdRp inhibitors against COVID-19:

Remdesivir and Favipiravir are other approved RdRp inhibitors in SARS-CoV-2 infection. Favipiravir was used as a post-exposure prophylactic agent, given orally for mild to moderate COVID-19 cases[7]. Remdesivir significantly decreases pulmonary damage and viral load in SARS CoV-2 infection. Hence it was approved to be given parenterally for the treatment of hospitalized patients with severe COVID-19 . Molnupiravir is effective against broader range of virus and also blocking COVID infection transmission in ferrets. It was approved to be given orally for both pre exposure prophylaxis and therapeutic use in COVID-19.

Pharmacokinetic property:

Molnupiravir is well absorbed orally and shows linear pharmacokinetics between doses of 50–1600 mg. Food decrease the rate of absorption of molnupiravir. It is not bound to plasma protein and well distributed in tissues. The half life of active metabolite is 3.3 hours. It should be administered twice daily to provide an adequate concentration in the respiratory tissues. It is eliminated in the urine as the active metabolite.

Therapeutic use of molnupiravir:

Molnupiravir is not a substitute for vaccination in individuals for whom COVID-19 vaccination and a booster dose are recommended. It is given as tablet 800mg BD for five days. It is safe and tolerable, highly effective at reducing nasopharyngeal SARS-CoV-2 infection[8].

Adverse effects:

Headache, nausea, and diarrhea are common side effects. Others like influenza like syndrome, back pain, rhinorrhea, hot flashes, and pain in extremity are present. Potential carcinogenic and teratogenic effects on sperm precursors and embryonic growth[9].

CONCLUSION:

The RdRp is an essential enzyme for COVID-19 replication and it plays key role in the pathophysiology of COVID-19. Molnupiravir targets RdRp and emergency approved drug for the treatment of patients with COVID-19. Based on clinical trial data, molnupiravir is effective for prophylaxis and therapeutic effect in patients with COVID-19.

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