Review article
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Molnupiravir, a New Antiviral Drug for the Treatment of COVID-19

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Abstract

The coronavirus disease first appeared in Wuhan, China in late December 2019 and spread very quickly to many countries around the world. A lot of antiviral drugs have been involved in treating COVID-19. Molnupiravir was the first oral antiviral drug and is a drug with anti-RNA polymerase effect and is still used today as an option in the treatment of patients with coronavirus disease 2019 (COVID-19). . In this review, we aimed to discuss the mechanism of action, safety, efficacy and clinical studies of molnupiravir in the treatment of patients with coronavirus disease.

Keywords: Pandemic, SARS-CoV-2, COVID-19, Molnupiravir

ABSTRACT

There is currently no definitive effective antiviral treatment for COVID-19, but many antiviral drugs have been studied since the first day of the pandemic and administered to patients for the treatment of Coronavirus, despite preliminary or conflicting results from clinical trials. In December 2021, based on the positive results of the MOVe-OUT trial, which was recently published in the New England Journal, it provided a license for molnupiravir, which has been approved and launched in many countries for use in groups of seriously ill patients at high risk of coronavirus disease 2019. Molnupiravir, a new oral antiviral drug, has recently received emergency use authorization (EUA) in the US, UK and India. Molnupiravir, administered orally; A major phase 3 clinical trial for coronavirus disease 2019 patients has delivered significant clinical benefits. (1) It was also the first oral antiviral agent approved for the treatment of coronavirus. We aimed to review and summarize current information about Molnupiravir, the new antiviral drug for COVID-19.

Pathophysiology of Covid 19

Coronaviruses have four main structural proteins, including spike, membrane, envelope, and nucleocapsid proteins. Coronaviruses invade the host cell through interaction between the spike protein and host cell receptors such as angiotensin-converting enzyme 2 and CD147. (2,3) RdRp is involved in Coronavirus replication in host cells and causes the production of Coronavirus with high mutagenicity and diversity. (4) After the first exposure, the immune system is triggered by cytotoxic cells, antibodies and interferons. In the later stages of the coronavirus, alveolar infiltration of T cells, neutrophils and macrophages causes the formation of cytokines such as interleukin (IL)-1, IL-6 and tumor necrosis factor-alpha. Cytokine storming leads to acute respiratory distress syndrome (ARDS) and multiple organ dysfunction. (4) Hyperinflammatory is also associated with the hypercoagulable state through overexpression of the tissue factor in the clotting cascade.

The mechanism of action of molnupiravir in COVID-19

In plasma, molnupyravir is converted by host esterases to the active nucleoside analogue (EIDD-1931). EIDD-1931 has been noted to inhibit a number of viruses, including Chikungunya virus, Venezuelan equine Encephalitis virus, Respiratory Syncytial virus, Norovirus, Influenza A and B viruses, Ebola virus and human Coronaviruses. EIDD-1931 spreads through several tissues and converts into the form of triphosphate. RdRp uses NHC triphosphate as the substrate instead of citidine-triphosphate and urine-triphosphate, which leads to the production of a mutated RNA. Molnupiravir is a more desirable electron donor, which

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changes the mandatory conditions for infectiousness. EIDD-1931 appears to affect the mitochondrial function of viruses, but in vitro studies have not shown a significant toxicity effect on mitochondrial function. (5) Molnupiravir inhibits the RdRp enzyme of SARS-CoV-2 and causes various errors in RNA virus replication. (6) In other words, molnupiravir-like remdesivir may reduce the pathogenesis and replication of coronaviruses. The results of the placement study showed that the limited mutation zone in the drug structure can cause inhibitory effects on the appearance of mutations associated with drug resistance of molnupiravir. Therefore, molnupiravir may be effective in treating remdesivir-resistant patients. (7)

It leads to the fact that viruses turn to molnupiravir instead of cytidine, leading to an error in the formation of RNA chains. Viruses with faulty RNA cannot infect cells (4). Molnupiravir is an analogue of a natural nucleoside molecule called cytidine. In hamster studies, the combination of molnupiravir with favipiravir has been shown to give superior results than its use alone in COVID-19-infected animals (4). The purpose of this article is to update our recent systematic review of molnupiravir and to give some practical tips and tricks regarding the use of molnupiravir for COVID-19 patients. Molnupiravir, which has also been used since October 15, 2021; We also examined its effectiveness compared to other drugs for the Coronavirus.

Clinical Studies

Phase 1 and phase 2 studies with molnupiravir have been concluded. Phase 3 studies are ongoing in different countries. The Phase 1 study was conducted in sixty-five healthy volunteers and there were no problems with absorption and distribution in the body, and side effects of headaches and diarrhea were seen in a very small group of participants. It is better tolerated than placebo (4). In the Phase 2 study, doses of 200, 400, 600, and 800 mg were given over 5.5 days. The rate of patients with virus positivity on day 3 was 20% in molnupiravir, 28% in the placebo group, 0% in the drug group on day 5 and 24% in the placebo group. In addition, all doses of the molnupiravir virus became negative on the 5th day. These results suggest that molnupiravir will rapidly reduce viral load in outpatients. (4). Phase 3 studies are ongoing in many countries. The results are expected to be announced in a few months. (4).

Application Method

Molnupiravir can be prescribed only by doctors to groups of mild to moderate patients. the recommended dose for those over 18 years of age is to take an 800 mg capsule of molnupiravir twice a day for 5 days, with or without food. Covid Tell patients that if they forget to take a dose of molnupiravir and the dose is usually within 10 hours of being taken, the patient should take this dose as soon as possible and continue the normal dosing schedule. If a patient misses a dose for more than 10 hours, the patient should not take the missed dose and instead compensate for the next dose at the regularly scheduled time. The patient is advised not to give two doses to compensate for a missed dose (8,9).

Side effect

Molnupiravir has been observed to cause cell death, mutations, does not cause serious side effects in liver cell lines and in animal studies. (4). The most common adverse reactions (incidence ≥ 1%) were nausea, vomiting, enteritis and dizziness, but similar to placebo. (8.9).

Table 1: Effects of the antiviral drug Molnupiravir

Alternative names	Lagevrio; EIDD-2801; MK-4482
Class	Antivirals; esters; hydroxylamines; pyrimidinones; ribonucleosides; small molecules
Mechanism of action	Viral replication inhibitors
Route of administration	Oral
Pharmacodynamics	Molnupiravir is hydrolysed to N-hydroxycytidine (NHC) which is phosphorylated to pharmacologically active N-hydroxycytidine triphosphate. Inhibits SARS-CoV-2 replication via viral error induction; robust in vitro and in vivo activity against SARS-CoV-2 retains activity against SARS-CoV-2 variants
Pharmacokinetics of NHC	t_{max} 1.5 h; a high-fat meal reduces C_{max} by 35%; does not bind to plasma proteins $t_{1/2}$ 3.3 h; gender, race, age, and kidney and liver impairment have no clinically relevant effect
Most frequent adverse events	Diarrhoea, nausea, dizziness, headache
ATC codes	
WHO ATC code	J05A-X (other antivirals)
EphMRA ATC code	J5B9 (antivirals, others)
Chemical name	[(2R, 3S, 4R, 5R)-3,4-dihydroxy-5-[4-(hydroxyamino)-2-oxopyrimidin-1-yl]oxolan-2-yl]methyl 2-methylpropanoate

High risk group:

1. Over sixty years of age,
2. Patients with active malignancy ,
3. Recipients of Kcell transplantation, patients withecological diseases
4. Patients with chronic kidney disease,
5. Patients with chronic liver disease,
6. Patients with immune-mediated inflammatory disorders (HIV/AIDS, organ transplant patients)
7. Some rare neurological conditions,
8. All patients with Down syndrome, sickle cell anemia,
9. Patients with obesity body mass index [BMI] ≥30 kg/m^2, It is contraindicated to patients who develop an allergy to the 10th drug due to the high risk.

Mild-to-moderate risk group: (10)

1. Fever, shortness of breath or hypoxia without upper respiratory symptoms
2. Patients with shortness of breath who have an exertion seizure, a respiratory rate of 20-≥30 beats per minute and/or a heart rate of <90-≥125 beats/minute <,
3. SpO_2 or additional oxygen >93% in room air
4. Patients without shortness of breath, respiratory failure, shock or multiple organ dysfunction/insufficiency at rest constitute the mild-to-moderate group.

Can we use Molnupiravir in pregnancy and nursing mothers?

Molnupiravir is not recommended for use during pregnancy. When considering molnupiravir for a pregnant individual, the health care provider who prescribes it should tell the pregnant individual about the known and potential benefits and potential risks of using molnupiravir during pregnancy. Breastfeeding during treatment with molnupiravir and for 4 days after the last dose is contraindicated. A breastfeeding individual may consider interrupting breastfeeding and expressing breast milk during treatment and for 4 days after the last dose of molnupiravir. (8)

The end:

Collectively, based on the evidence currently available, molnupiravir appears to be a highly effective agent in reducing the composition of death and hospitalization or death in high-risk adult patients with COVID-19 at a relatively low cost. The role of molnupiravirin is available orally at a lower cost, especially in outpatient settings. Well-designed randomized clinical trials are needed to confirm the therapeutic effects of molnupiravir in patients with Coronavirus in the future.

Application

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