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Molnupiravir-An Antiviral Medication for the Management of COVID-19

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Abstract

At present, despite the production of a variety of effective and available vaccines to prevent COVID-19, there are no effective antiviral drugs to combat the disease. While some of the drugs have recently been given an emergency use authorizations for COVID-19, conflicting information can be seen in some cases. Thus, a simple oral antiviral drug development has been an elusive target since the beginning of this pandemic. This review with help of some DATA base searching motors as PubMed, Google scholar spends on some clinical and basic pharmacology of Molnupiravir as antiviral drug.

This review aims to evaluate the efficacy, safety, and clinical trials of molnupiravir administration in the treatment of patients with COVID-19. According to results of this review the safety, tolerability, and antiviral effects of molnupiravir have been shown to be effective in many clinical trials to reduce proliferation, accelerate virus clearance, and induce infection in patients with COVID- 19. Molnupiravir was originally designed to inhibit replication of influenza virus. It has subsequently been tested for activity against other RNA viruses. It is quickly cleaved in plasma to EIDD-1931 by host esterases, which is the active form of molnupiravir. After distribution in various tissues, it is eventually converted to the corresponding 59-triphosphate by host kinases, the active antiviral agent. Inside the host cell lines, molnupiravir is converted to molnupiravir triphosphate. When the coronaviruses tries to replicate, molnupiravir triphosphate is incorporated into the viral RNA instead of the nucleoside cytidine, causing a mutation. Recently, treatment with molnupiravir in phase III trials reduced the risk of hospitalization or death by up to 50% for patients with mild to moderate COVID-19 symptoms12. In this regard, there is a need for further investigation in patients with the underlying disease and also drug-drug interaction studies along with other treatments in large-scale clinical trial studies.

Keywords: Mild and Moderate COVID-19 Infections; Antiviral Drugs; Molnupiravir; Clinical Trials; Review

Introduction

On December 31, 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first identified in Wuhan, China and has rapidly spread too many countries around the world. While the development of a variety of vaccines will lead to long-term immunity in individuals, researchers are working to produce a variety of antiviral compounds that can be used to counter novel viruses. While vaccines were a success story, disadvantages such as short-

term immunity, the need to inject multiple doses, and the occurrence of some allergic side effects, have led researchers to design an oral agent formula because of its ease of use. Many antiviral drugs have so far failed to show beneficial effects or showed contradictory results. Although existing antiviral drugs increase the recovery rate of patients with COVID-19, they do not appear to have a significant effect on reducing mortality [1]. Therefore, researchers are developing an effective formulation of antiviral drugs that can be easily consumed under emergency situation.

Molnupiravir is a medication therapy with anti-RNA polymerase activity that is prescribed in the form of oral tablets for patients newly diagnosed with COVID- 19 and has shown high efficacy so far [1,2]. The antiviral function of molnupiravir is mediated by the presentation of transcription errors during viral RNA replication. Mulnopiravir was first identified as a broad-spectrum antiviral compound. It was used as an effective combination in the treatment of hepatitis C. Later, the use of this compound was limited due to the possible side effects of long-term use [3,4]. Molnupiravir are taken to decrease the severity and duration of flu symptoms. With the advent of the COVID-19 epidemic, the focus of molnupiravir use has shifted to treating those infected with the virus.

Molnupiravir continues to allow viral RNA strands to grow. However, the wrong nucleosides attach to this chain and lead to many mutations. In other words, the chain is destroyed, the compound is broken down in the body, and the part that interferes with the replication of the virus is absorbed into the bloodstream. The full effectiveness of this drug is still in doubt, and severe side effects are possible due to the mutagenic mechanism of molnupiravir (Figure 1).

The greatest advantage of molnupiravir is that the RNA-dependent RNA polymerase has no equivalent in the human body [5-7].

In this line, Abdelnabi, et al. investigated the combined effects of molnupiravir and favipiravir treatments against SARS-CoV-2 infection on Syrian hamster infection model. The combination of less than optimal doses of two oral drugs resulted in a marked antiviral activity in their hamster infection model. When the first dose was given just before infection, the titer of the infectious virus dropped significantly in 10 of the 16 animals treated with these drugs [8]. This effective result may be explained by the increased accumulation of mutations in the combination of the two drugs compared to the use of either alone, and may allow the use of lower doses of the compounds in clinical settings.

In the review, we summarized the results of published literature on clinical evidence about the safety and efficacy of the molnupiravir administration in the treatment of COVID-19 patients.

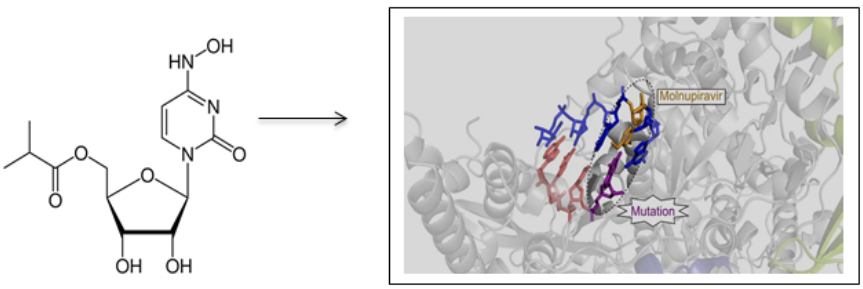

Figure 1: The mechanism of action of molnupiravir: molnupiravir (yellow) is located in viral RNA, where it causes a (purple) mutation that eventually prevents the COVID- 19 virus from replicating [9].

Antiviral activity of Molnupiravir against COVID-19

Molnupiravir (EIDD-2801, MK-4482) is being developed by Merck and Ridgeback for the treatment of mild to moderate COVID-19 in adult patients. It is an orally bioavailable prodrug of the nucleoside analogue β-D-N4-hydroxycytidine (NHC, also named as EIDD-1931), which is the form in which it's recognized by the RNA polymerase enzyme [10].

Molnupiravir was originally designed to inhibit replication of influenza virus. It has subsequently been tested for activity against other RNA viruses [5]. As shown in Figure 2, molnupiravir is quickly cleaved in plasma to EIDD-1931 by host esterases, which is the active form of molnupiravir. After distribution in various tissues, it is eventually converted to the corresponding 59-triphosphate by host kinases, the active antiviral agent [5].

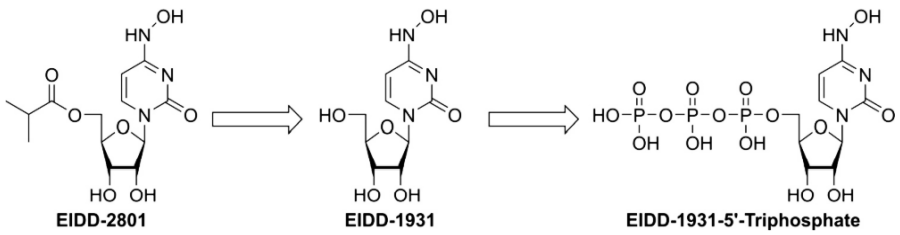

Figure 2: Molecular mechanism of molnupiravir in plasma [11].

Inside the host cell lines, molnupiravir is converted to molnupiravir triphosphate. When the coronaviruses tries to replicate, molnupiravir triphosphate is incorporated into the viral RNA instead of the nucleoside cytidine, causing a mutation. Recently, treatment with molnupiravir in phase III trials reduced the risk of hospitalization or death by up to 50% for patients with mild to moderate COVID-19 symptoms [12].

The effect of this drug on the COVID-19 virus cycle before the onset of symptoms was greater than 24 and 48 hours after infection. The results of studies have shown that molnupiravir is active in several clinical stages of SARS-CoV-2 including prevention, treatment, and prevention of transmission. In intracellular conditions, molnupiravir is hydrolyzed to N4-hydroxycytidine that is phosphorylated in tissue to the active 5'-triphosphate form, and incorporated into respiratory viruses' genome, resulting in the proliferation of inactivating mutations, known as viral error catastrophe [13].

This drug can increase guanine (G) to adenine (A) and cytosine (C) to uracil (U) transition mutations in replicating coronaviruses [14]. The frequency of mutations ultimately leads to the production of nonfunctional genomes that justify the antiviral effect. Other antiviral medicines, such as ribavirin or favipiravir, have similar mechanisms. However, these medications were less lethal than molnupiravir with EC50 values [15]. Factors determining the potency of antiviral drugs by interactions with RNA-dependent RNA polymerase and the exact nature of its mechanism of action still need further investigation. In general, the mechanism of molnupiravir mutagenesis against respiratory viruses is shown in Figure 3.

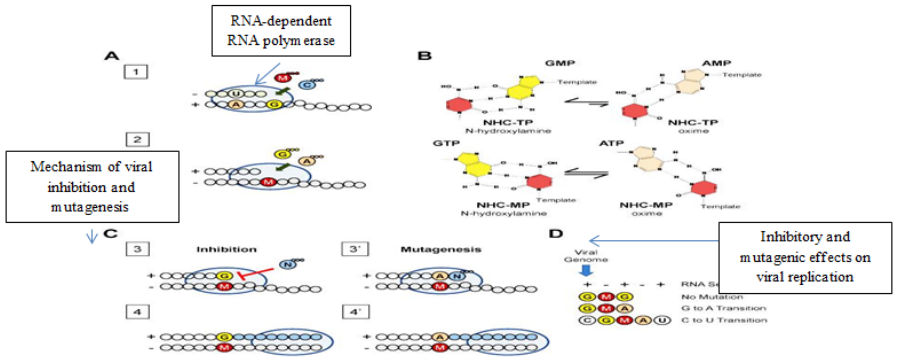

Figure 3: Mechanism of mutation of molnupiravir tablets on the replication and transcription of the SARS-CoV-2 genome (works by inducing mutagenesis in viral RNA). A, C, G, and U are acronyms for natural nucleotide bases. M: molnupiravir, MP: monophosphate, NHC-MP: β-D-N4-hydroxycytidine monophosphate, NHC-TP: β-D-N4-hydroxycytidine 5'-triphosphate. (±): RNA sense. This four-step mutagenesis mechanism probably can explain the antiviral activity of Molnupiravir [16].

Animal Models

Molnupiravir change the viral genetic material and introduce errors to prevent replication and transcription of the viral genome of coronaviruses in animal infected models, and culture media containing airway epithelial cells. Wahl, et al. investigated the effect of the therapeutic and prophylactic administration of molnupiravir on pathogenesis of SARS-CoV-2. Their results showed that therapeutic and prophylactic administration of molnupiravir markedly inhibited SARS-CoV-2 replication in vivo, and thus has considerable potential for the prevention and treatment of COVID-19 [17].

In other study, Sheahan, et al. [18] reported that molnupiravir significantly exhibited antiviral activity when administered

2 hours before, or 12 or 24 h after SARS-CoV-2 infections can produce good consistency approaching that obtained by observing five days a week (by the returned body weight and improved pulmonary function during the five-day observation).

Abdelnabi, et al. [8] stated that molnupiravir inhibits replication of the emerging SARS-CoV-2 variants including B.1-G, B.1.1.7, or the B.1.351 of concern in a Hamster infection model. The obtained results showed that the treated animals' lungs did not have focal bronchopneumonia, no or focal perivascular inflammation, and no virchow–robin space edema8. Histopathological assessments in this study are shown in Figure 4.

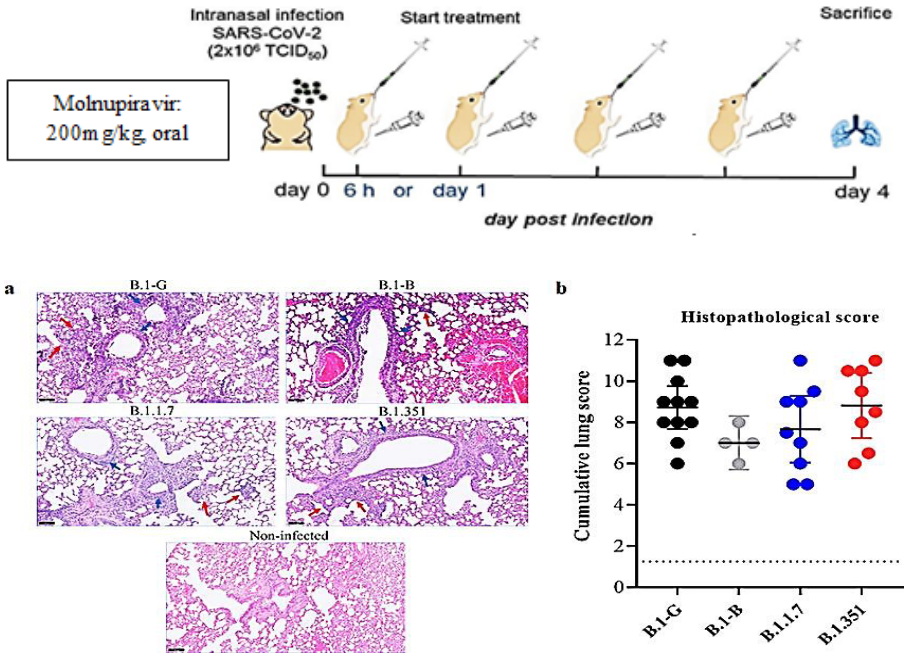

Figure 4: Antiviral activity of molnupiravir in Syrian hamsters infected with different SARS-CoV-2 variants. Evaluate the histopathological image from this study showed no or very focal bronchopneumonia, no or focal perivascular inflammation, and no perivascular edema [8].

Human Body

Review of the literatures showed the positive impact of molnupiravir administration to be safe and well tolerated in phase 1 and 2 trials in the treatment of patients with mild to moderate COVID-19. Phase 3 studies are ongoing to evaluate the effect of molnupiravir on illness duration and symptom profile, severity, risk factors emergency department visits, and hospitalizations. In this line, Mahase (2021) stated that in accordance with the claims of the Merck company, Molnupiravir reduces risk of hospital admission or death by 50% in patients at risk COVID-19 by the timing of symptom onset, underlying risk factors, or variant types (gamma, delta, and mu) [19].

Clinical Trials of Molnupiravir

Pre-Clinical Test

Painter, et al. [20] investigated the effects of molnupiravir on human safety and tolerability via pharmacokinetics of novel broad-spectrum oral antiviral agent against severe acute respiratory syndrome coronavirus. In this first-inhuman, phase 1, randomized, double-blind, placebo-controlled study, single and multiple doses of molnupiravir were used for 5 days in the treatment of 202 patients with mild to moderate COVID-19. The results showed that the treated groups with administration of 600 to 800 mg of molnupiravir was very effective in reducing virus infection and has good safety characteristics and tolerance with similar numbers of adverse events across all groups. There were no significant negative signs in the dose-related procedure used in the clinical laboratory, vital signs observed, and electrocardiogram data.

Ongoing Studies

Human studies that have reported the results from phase 1 to 3 studies including completed, incomplete, and several ongoing trials were ordered in Table 1.

Clinical Phase	Treated groups	Administrated dosages	Clinical progression outcomes	Ref
Phase 1	healthy volunteers (n = 130)	A range of 50e800 mg twice daily	After oral administration, molnupiravir was well tolerated and there was a dose proportional pharmacokinetics following administration. The most common side effects were headache, pruritic rash, and diarrhea.	[20]
Phase 2	An open label randomized controlled with 18 adults within 5 days of COVID-19 symptom onset	300, 600 and 800 mg dosages of molnupiravir twice daily for 5 days by oral route.	Safety and tolerability of multiple ascending doses to recommend a dose for the phase-II trial.	[3]
Phase 2	An open label randomized Controlled with 202 and more than 2000 treated participants with onsets Of COVID-19 symptoms within 7 days.	Twice daily oral doses of 200 mg, 400 mg and 800 mg molnupiravir for 5 days.	Regarding tolerability, overall, very few, low grade adverse events were noted in this study. Hypoxia, decreased oxygen saturation, cerebrovascular accident and acute respiratory failure were reported in a small number of patients. In final, they stated that molnupiravir had a favorable safety and tolerability profile.	[21,22]
Phase 3	A double-blind, randomized study on 1850 non-hospitalized adult (18 years or older) participants with COVID-19		The results showed a significant reduction in risk of hospital admission or death by 50% at day 29. The efficacy of molnupiravir was unaffected by the SARS-CoV-2 variants including gamma, delta or mu.	[19,23,24]
Phase 3	A double-blind, randomized study on 304 hospitalized adult (18 years or older) participants with COVID-19. A multicentric, randomized, double-blind, placebo-controlled Study (n=1332).	Ongoing	The primary studies results showed a clinical benefit in hospitalized patients.	[23,24]
Phase 3	About 741 mild COVID-19 patients	Ongoing studies	No death reported in this study. Nausea, diarrhea and headache were most common side effect reported with mild severity.	[25]
Phase 3	More than 300 persons with in mild COVID-19 patients from India	800 mg every 12 h (twice daily) for 5 days	Primary results showed a higher RT-PCR negativity and faster clinical improvement, clinical and viral recovery in treated groups with molnupiravir. 6.5% treated peoples with molnupiravir had adverse events. There has been 1 hospitalization in treated group with molnupiravir.	[25]

Phase 3	mild COVID-19 patients from India More than 300 persons with in		The results showed a faster clinical and viral recovery (RT-PCR negativity) with relatively good safety profile; exhibiting a significant reduction in virus titers only after two days from administration.	[25]
Phase 3	Originally planned for a total of 1218-1220 patients with mild COVID-19	800 mg for two weeks	No beneficial effects were seen.	[25]

Table 1: The interim results, stopped, and ongoing studies on treated groups with molnupiravir in COVID-19 to date.

Discussion

The conducted preclinical and clinical studies confirm the efficacy and safety of oral molnupiravir as an antiviral therapy for the treatment of mild to moderate patients with COVID- 19 in terms of mortality and hospitalization rates. It reduced the length of hospital stay and the spread of COVID -19 infections in many stages of clinical trials, especially in its early stages. On the subject of infectious diseases, Painter, et al. stated that the use of molnupiravir was very effective in treating seasonal and pandemic influenza infections and in preventing the transmission of SARS-CoV-2. The lowest effective doses against seasonal and pandemic influenza were 2.3 and 7 mg/kg body weight. However, in order to suppress the symptoms of SARS-CoV-2 disease (lung viral loads and in improving pulmonary function), the required amount of molnupiravir is 100- 500 mg/kg body weight [20].

This drug can be used on an outpatient basis in patients with COVID- 19. Compared to manufactured vaccines, this drug does not require complex preparation steps and no special treatment protocols are required to prescribe it to patients. However, in patients with COVID -19 with underlying diseases (such as diabetes, obesity, and cardiovascular disease), more pilot-scale tests are needed [25]. The results also showed that molnupiravir in different stages of clinical trials had the fewest side effects compared to other drugs effective in reducing COVID-19 infection at least in short-terms. However, some researchers did raise concerns about the safety of molnupiravir that works by causing mutations. Further studies on the mutagenic effects of the drug should be performed in patients currently receiving the vaccine [26,27].

Additionally, they recommend monitoring to assess potential genotoxic side effects. However, by conducting in vivo tests, Merck has listed molnupiravir as a non-mutagenic medicine in a research program [25]. The occurrence of drug interactions, the effect of this drug on patients in the very advanced stages of COVID-19 disease, as well as prescribing to patients who did not show specific symptoms in the early stages are some of the issues that need to be further investigated.

Finally, the study of the effect of molnupiravir on a wide range of COVID-19 virus variants can shed more light on the importance of the time factor in clinical trials. In the study conducted by Abdelnabi, et al. the effects of molnupiravir and favipiravir administration on lung infection were investigated in a SARS-CoV-2 Syrian hamster infection models. A significant reduction in the number of viruses in lung tissue is apparent 1 day after the start of treatment, which may explain the pronounced antiviral potency of the combination8. They also stated that molnupiravir was effective against COVID- 19 infections with each of the variants and therefore may have potential combating current and future emerging variants of concern8. Compared to other drug treatments, the use of molnupiravir in different clinical phases had almost similar results in terms of adverse effects and severity of viral infection [20]. There was no evidence of toxicity in the various doses of molnupiravir used in tissues and blood. Co-administration of molnupiravir with food had no effect on therapeutic exposure in terms of pharmacokinetic studies.

Conclusion

The safety, tolerability, and antiviral effects of molnupiravir have been shown to be effective in many clinical trials to reduce proliferation, accelerate virus clearance, and induce infection in patients with COVID- 19. It reduced the length of hospital stay and the spread of COVID -19 infections in many stages of clinical trials, especially in its early stages. The results also showed that molnupiravir in different stages of clinical trials had the fewest side effects compared to other drugs effective in reducing COVID-19 infection at least in short-terms.. Further studies on the mutagenic effects of the drug should be performed in patients currently receiving the vaccine. Additionally, they recommend monitoring to assess potential genotoxic side effects.

Finally, the study of the effect of molnupiravir on a wide range of COVID-19 virus variants can shed more light on the importance of the time factor in clinical trials. In this

regard, there is a need for further investigation in patients with the underlying disease and also drug-drug interaction studies along with other treatments in large-scale clinical trial studies.

Conflict of Interest

The authors declare no competing interests.

Ethical Statement

Non applicable

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