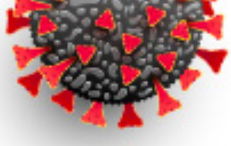
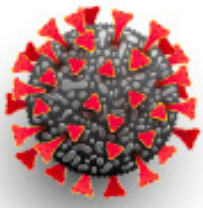
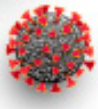


MEDICAL COLLEGE OF WISCONSIN SCHOOL OF PHARMACY STUDENT WRITING CLUB:

Molnupiravir: Review of a New Oral Antiviral Agent Approved for Emergency Use Authorization in the United States for Coronavirus Disease 2019





by Vanessa Lei, PharmD Candidate 2023, Payeng Lor, PharmD Candidate 2023, Vanessa Sanchez, PharmD Candidate 2023, Kong Choua Thao, PharmD Candidate 2023, Zachary Hovis, PharmD, BCACP

Coronavirus disease 2019 (COVID-19) is a severe acute respiratory illness caused by the novel coronavirus SARS-CoV-2 and resulting in an ongoing global pandemic. As of January 2022, SARS CoV-2 totaled 64,720,612 cases and 843,718 deaths in the U.S. alone.[1] While all populations are at risk of contracting COVID-19, people who are older, are immunocompromised, or who have certain comorbidities (e.g. cardiovascular disease, diabetes, or chronic lung disease) have a much higher risk of progressing to severe disease and hospitalization.[2] Due to the high transmissibility and infectious nature of COVID-19, many preventive measures, such as the use of masks in public settings and social distancing, have been put into place nationally. These preventive measures play an essential role in combating widespread transmission of the novel coronavirus. Additionally, the development of numerous mRNA vaccines against COVID-19 have resulted in reduced transmission and hospitalization. Phase three trial data for one of the mRNA vaccines demonstrated an effectiveness rate of 94.1% for preventing laboratory-confirmed COVID-19 following full vaccination and 90% effectiveness rate six months post vaccination.[3-4] As of this writing on January 22, 2022, 80.2% of the U.S. population has received at least one dose of a COVID-19 vaccine.[5] While rates of vaccination are high, many individuals remain hesitant to get vaccinated due to various psychosocial reasons, with the most prevalent being concerns about vaccine side effects, and mistrust of COVID-19 vaccines in terms of safety or efficacy.[6] Those who are unvaccinated continue to experience high rates of hospitalizations and deaths, with unvaccinated individuals being 16 times more likely to become hospitalized and 15 times more likely to die from COVID-19 compared to fully vaccinated individuals.[7]

While highly effective, vaccines alone are inadequate for reducing the full disease burden of COVID-19 in the United States, given the limitations of vaccine uptake.[3,8] This created a need for a therapy that could reduce the risk of disease progression in patients with mild to moderate COVID-19. This led to the emergence of several new oral antiviral agents such as molnupiravir, nirmatrelvir, and ritonavir for treatment. Molnupiravir was the first oral antiviral agent to receive authorization to treat COVID-19 in the world, approved on November 4, 2021, by the United Kingdom Medicine and Healthcare Product Regulatory Agency.[9] This was followed by the U.S. Food and Drug Administration (FDA) issuing an emergency use authorization (EUA) on December 23, 2021, for the use of molnupiravir in COVID-positive patients with high risk of progressing to severe COVID-19.[10] This paper aims to evaluate the safety and efficacy of molnupiravir for treatment of mild to moderate COVID-19 based on current research and literature.

Market Analysis

As of this writing, remdesivir is currently the only FDA-approved medication for the treatment of COVID-19 infections in both hospitalized and outpatient patients.[11-12] It is administered intravenously and has demonstrated superiority in reducing recovery time for hospitalized patients with severe cases when compared to placebo.[13-14] Additionally, remdesivir demonstrated an 87% reduction in risk of hospitalization and death in non-hospitalized patients who were at an increased risk for worsening progression of COVID-19 with a three-day treatment course.[16] Given remdesivir's route of administration, a need still exists for a less invasive outpatient antiviral treatment option that would reduce the risk of disease progression in patients with mild to moderate infections.[3,15] Initially, hydroxychloroquine was thought to be beneficial for the treatment of COVID-19 and was given EUA by the FDA in March 2020, but that EUA was rescinded in June 2020 due to non-significant data after more extensive review.[17] In an observational study that evaluated the benefit of hydroxychloroquine for hospitalized patients, no significant difference in the end composite of intubation or death was observed among the two groups.[18] In another study focusing on the treatment for mild to moderate COVID-19 cases, hydroxychloroquine failed to show significant benefits and had an increase in cardiac adverse effects compared to the non-recipient group.[19] The ORCHID trial, designed to evaluate the efficacy and safety of hydroxychloroquine for COVID-19 patients, was discontinued as there was no clear benefit.[17]

As evidenced by the increasing number of patients hospitalized, partly due to the contagious Omicron COVID-19 variant, novel oral antiviral therapies are an

important avenue to explore to reduce the burden on health care systems. There are a few promising oral therapies with positive early results in current literature, including molnupiravir, nirmatrelvir, and ritonavir.[9] In the rest of this article, we will further explore molnupiravir.

Mechanism of Action

Molnupiravir works by introducing errors into the SARS-CoV-2 virus's genetic code, which prevents viral replication. Specifically, molnupiravir is a synthetic ribonucleoside derivative N-hydroxycytidine (NHC) prodrug that circulates systemically and is phosphorylated intracellularly to NHC triphosphate. NHC triphosphate is integrated into the viral RNA which misdirects the viral polymerase to incorporate either guanosine or adenosine leading to deleterious errors.[3,22] The accumulation of deleterious errors leads to a viral error catastrophe preventing replication.[23] Lee et al created a visual representation of the mechanism of action of molnupiravir.[24]

Pharmacokinetics

The pharmacokinetics of molnupiravir have been studied in healthy subjects in both single and multiple doses in fed and fasting states. Subjects include humans, mice, rats, dogs, monkeys, and ferrets.[25] A summary of the pharmacokinetics can be seen in Table 1.

Absorption:

Molnupiravir is a 5' -isobutyrate ester prodrug cleaved by esterase in the intestine and liver to be converted into NHC.[25] The absorption and conversion process of molnupiravir occurs very rapidly and maximum serum concentration is reached at around 1.5 hours. Administration of molnupiravir with food will decrease maximum serum concentration by 35% with no effect on area under the curve (AUC). Molnupiravir is reported to be well tolerated with minimal adverse effects.[22,24]

Distribution:

The mean volume of distribution of Molnupiravir was 142 liters when taking 800 mg every 12 hours.[22] In most species, tissues with the highest exposures include the lung and spleen, and the tissue with the lowest levels was the brain. The plasma protein binding of molnupiravir was not assessed since the molecule is not stable in plasma.[22,25]

Metabolism:

In vivo metabolism studies of molnupiravir were performed on Wistar Han rats and male intact beagle dogs.[22] After oral administration, there was a low recovery of molnupiravir and its metabolites in excreted waste, indicating how well molnupiravir was absorbed. It was confirmed in an in vitro study that the majority of the molnupiravir was metabolized to pyrimidine metabolites, with the major metabolite being uridine and the minor metabolites being cytidine monophosphate and uridine monophosphate. These metabolites were integrated into the endogenous pyrimidine pool, hence the low recovery in excreted waste.

Elimination:

Molnupiravir is excreted in urine as NHC and endogenous pyrimidine nucleosides, uridine or cytidine. Molnupiravir is calculated to have a half-life of about 3 hours, with the majority of the drug being excreted within the first 4 hours. There is no dose adjustment needed in patients with any degree of renal or hepatic impairment as there was no meaningful impact on the pharmacokinetics of NHC. It is important to note that studies have not been evaluated in patients with eGFR less than 30 mL/min/1.73m^2 or on dialysis, severe renal impairment, and end-stage renal disease (ESRD).[22,25]

Pharmacodynamics

A humanized mouse model (immunodeficient mice who were implanted with human lung tissue) was performed using infected lung only mice.[24] The model demonstrated a significant reduction of in vivo replication of SARS-CoV-2 in mice with infected lungs when molnupiravir was given prophylactically at a dose of 500 mg/kg.[24,25] Therapeutic administration also demonstrated reduction in SARS-CoV-2 but was largely dependent on time of treatment initiation.[27] Additionally, treatment with molnupiravir in infected ferrets displayed a significant reduction in SARS-CoV-2 viral load within 12 hours of initiating treatment, and furthermore, blocked transmission of SARS-CoV-2 to untreated ferrets after 30 hours of initiating treatment.[22, 25- 27]

Clinical Data

The phase three randomized controlled trial MOVe-OUT evaluated the safety and efficacy of molnupiravir in non-hospitalized patients infected with mild-moderate COVID-19 compared to placebo.[3] MOVe-OUT included 1,433 participants who were enrolled at 107 sites from 20 different countries and underwent randomization in a 1:1 ratio for either molnupiravir treatment or placebo treatment. Participants were to take 800 mg of molnupiravir orally twice daily for a period of five days, or placebo, and were followed through day 29. Inclusion criteria were current SARS-CoV-2 infection that had been laboratory confirmed with mild-moderate signs and symptoms occurring no more than five days prior. Additionally, eligible participants had to have at least one additional risk factor for the development of a serious COVID-19 infection such as age greater than 60 years old, active cancer, chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), obesity (BMI ≥ 30 kg/m^2), serious heart conditions (heart failure,

TABLE 1. Pharmacokinetic of Molnupiravir after multiple oral administration of 800 mg every 12-hr[22]

Absorption	
T_{max} (hr)	1.50 [1.00 - 2.02]
Effect of food	35% reduction in C_{max}, no effect on AUC
Distribution	
Plasma Protein Binding	0%
Volume of Distribution (L)	142
Elimination	
T1/2 (hr)	3.3
Clearance (L/hr)	76.9
Fraction of dose excreted in urine over the time interval of 0-12 hr	3% as NHC, 81.6% as endogenous pyrimidine nucleoside

AUC = Area under the curve, NHC = N-hydroxycytidine

CAD, cardiomyopathies), or diabetes mellitus. Key exclusion criteria included anticipated hospitalization within the next 48 hours, dialysis, an estimated glomerular filtration rate (eGFR) less than 30 mL/min/1.73 m^2, pregnancy, unwillingness to use contraception during the intervention period, severe neutropenia, low platelet count less than 100,000 per mcL, and vaccination against SARS-CoV-2. Baseline characteristics for both groups were statistically similar.

The primary efficacy endpoint for the trial was the incidence of hospitalization for any cause, or death, through day 29.[3] The primary safety endpoint was the incidence of adverse events with patients being evaluated for any drops in platelet count (less than 50,000 per mcL) and potential hepatotoxicity induced by the medication. Given data from the planned interim analysis at 50% enrollment, the MOVe-OUT trial was recommended to end recruitment early given positive efficacy results by an independent data monitoring committee. After the 29-day period, the primary efficacy endpoint was significantly lower in the molnupiravir group (7.3%) compared to the placebo group (14.1%) (P = 0.001). The percentage of participants with at least one adverse event was similar in both groups (30.4% in the molnupiravir group vs. 33.0% in the placebo). Deaths were reported less frequently in the molnupiravir group (2 deaths) compared to the placebo group (12 deaths) (95% CI: -2.7 to -5). Results were consistent in all subgroups based on gender, race, baseline COVID severity, and the specified risk factor (i.e. DM, age, CVD).

Conclusion

Molnupiravir is the first oral antiviral medication that has data supporting its safety and efficacy in treating mild to moderate SARS-CoV-2 infection. The importance of having an outpatient oral antiviral therapeutic option for high-risk individuals represents an important treatment breakthrough in the global fight to reduce the burden of COVID-19. Further studies should be done to evaluate the potential benefits of molnupiravir for the treatment of COVID-19 infections among vaccinated individuals, and as well as repeat infections, to help better inform clinical decision making.

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