Molnupiravir

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Molnupiravir is the oral prodrug of beta-D-N4-hydroxycytidine (NHC), a ribonucleoside that has shown antiviral activity against SARS-CoV-2 in vitro and in clinical trials.\(^1\)\(^2\) NHC uptake by viral RNA-dependent RNA-polymerases results in viral mutations and lethal mutagenesis.\(^3\)\(^4\) On December 23, 2021, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for molnupiravir for the treatment of adults with mild to moderate COVID-19 who are within 5 days of symptom onset, who are at high risk of progressing to severe disease, and for whom alternative antiviral therapies are not accessible or clinically appropriate.\(^5\)\(^6\)

As a mutagenic ribonucleoside antiviral agent, there is a theoretical risk that molnupiravir will be metabolized by the human host cell and incorporated into the host DNA, leading to mutations. Molnupiravir has been evaluated in 2 in vivo rodent mutagenicity assays. One study produced equivocal results. In the other study, there was no evidence for mutagenicity.\(^6\) The FDA concluded that, based on the available genotoxicity data and the 5-day duration of treatment, molnupiravir has a low risk for genotoxicity.\(^6\) In addition, there have been concerns about the potential effects of molnupiravir on SARS-CoV-2 mutation rates; the FDA has required that the manufacturer monitor genomic databases for the emergence of SARS-CoV-2 variants.

Recommendations

• The COVID-19 Treatment Guidelines Panel (the Panel) recommends using molnupiravir 800 mg orally (PO) twice daily for 5 days as an alternative therapy in nonhospitalized patients aged ≥18 years with mild to moderate COVID-19 who are at high risk of disease progression ONLY when ritonavir-boosted nirmatrelvir (Paxlovid) and remdesivir are not available, feasible to use, or clinically appropriate; treatment should be initiated as soon as possible and within 5 days of symptom onset (CIIa).

• The Panel recommends against the use of molnupiravir for the treatment of COVID-19 in pregnant patients unless there are no other options and therapy is clearly indicated (AIII).

• People who engage in sexual activity that may result in conception should use effective contraception during and following treatment with molnupiravir. For more details, see Considerations in Sexually Active Individuals below.

Molnupiravir may be used in patients who are hospitalized for a diagnosis other than COVID-19, provided they have mild to moderate COVID-19 and are at high risk of progressing to severe disease. For the Panel’s recommendations on preferred and alternative antiviral therapies for outpatients with COVID-19, see Therapeutic Management of Nonhospitalized Adults With COVID-19.

Rationale

The MOVe-OUT trial enrolled high-risk, unvaccinated, nonhospitalized adults and reported that molnupiravir reduced the rate of hospitalization or death among these patients by 31% compared to placebo.\(^7\) However, this trial occurred before the emergence of the Omicron variant and its subvariants. A secondary analysis of the patients who required hospitalization during the trial found a reduced need for respiratory interventions among those who were randomized to receive molnupiravir compared to those who received placebo.\(^8\) Molnupiravir has shown activity against the Omicron subvariants in vitro and in animal studies.\(^2\)\(^9\)\(^-\)\(^11\)
Although the different COVID-19 treatment options have not been directly compared in clinical trials, the Panel recommends using molnupiravir only when ritonavir-boosted nirmatrelvir and remdesivir are not available or cannot be given, because molnupiravir appears to have lower efficacy than these other options.

Whether molnupiravir reduces the risk of hospitalization or death in people who are vaccinated and at high risk of progressing to severe COVID-19 is unclear. Some observational studies have evaluated the effect of molnupiravir in nonhospitalized or hospitalized adults who are at high risk of progressing to severe disease, including some patients who received COVID-19 vaccines, but these studies have limitations.12-14 For treatment considerations for vaccinated individuals, see Therapeutic Management of Nonhospitalized Adults With COVID-19.

The Panel **recommends against** the use of molnupiravir for the treatment of COVID-19 in pregnant patients unless there are no other options and therapy is clearly indicated (AIII). For more details, see Considerations in Pregnancy below.

**Additional Considerations**

- Patients should complete the 5-day treatment course of molnupiravir. It is unknown whether a shorter course is less effective or associated with the emergence of molnupiravir-resistant mutations.
- If a patient requires hospitalization after starting treatment, the full treatment course of molnupiravir can be completed at the health care provider’s discretion.
- There are no data on using combination antiviral therapies or combinations of antiviral agents and anti-SARS-CoV-2 monoclonal antibodies for the treatment of nonhospitalized patients with COVID-19. Clinical trials are needed to determine whether combination therapy has a role in the treatment of SARS-CoV-2 infection.
- Patients who are severely immunocompromised can experience prolonged periods of SARS-CoV-2 replication, which may lead to rapid viral evolution. There are theoretical concerns that using a single antiviral agent in these patients may produce antiviral-resistant viruses. Additional studies are needed to assess this risk. The role of combination antiviral therapy in treating patients who are severely immunocompromised is not yet known. See Special Considerations in People Who Are Immunocompromised for more information.
- It is not yet known how often viral rebound occurs in patients who have completed treatment with molnupiravir.

**Considerations in Sexually Active Individuals**

For individuals of childbearing potential, clinicians should assess the patient’s pregnancy status before initiating molnupiravir.

Patients of childbearing potential should be counseled about abstaining from sex or using reliable contraception for the duration of therapy and for up to 4 days after taking molnupiravir. Reproductive toxicity has been reported in animal studies of molnupiravir, and molnupiravir may be mutagenic during pregnancy.

The FDA EUA states that men of reproductive potential who are sexually active with individuals of childbearing potential should be counseled to abstain from sex or use a reliable method of contraception for the duration of treatment and for at least 3 months after the last dose of molnupiravir.
Considerations in Pregnancy

The Panel **recommends against** the use of molnupiravir for the treatment of COVID-19 in pregnant patients unless there are no other options and therapy is clearly indicated (AIII).

The FDA EUA states that molnupiravir is not recommended for use in pregnant patients because fetal toxicity has been reported in animal studies of molnupiravir. However, when other therapies are not available, pregnant people with COVID-19 who are at high risk of progressing to severe disease may reasonably choose molnupiravir therapy after being fully informed of the potential risks, particularly if they are beyond the time of embryogenesis (i.e., >10 weeks’ gestation). The patient should also be informed about the pregnancy surveillance program and offered the opportunity to participate.

There is currently a lack of data on the use of molnupiravir in lactating people, and molnupiravir may cause adverse effects in infants who are exposed to the drug through breastfeeding. Because of this, the FDA EUA states that lactating people should not breastfeed their infants during treatment with molnupiravir and for 4 days after the final dose. Pumping and discarding breast milk to maintain supply during this time is recommended.

Considerations in Children

The MOVe-OUT trial excluded participants aged <18 years. There are no data available on the use of molnupiravir in children aged <18 years. Molnupiravir is not authorized for use in those aged <18 years due to potential effects on bone and cartilage growth.

Monitoring, Adverse Effects, and Drug-Drug Interactions

The most common adverse effects of molnupiravir are diarrhea, nausea, and dizziness. Based on in vitro studies, neither molnupiravir nor its active metabolite NHC are inhibitors or inducers of major drug-metabolizing enzymes or inhibitors of major drug transporters. According to the EUA, no drug-drug interactions have been identified for molnupiravir.

Clinical Data

MOVe-OUT was a multinational, Phase 3 trial that evaluated the use of molnupiravir in unvaccinated, nonhospitalized adults with mild to moderate COVID-19 who were at high risk of progressing to severe COVID-19 and enrolled within 5 days of symptom onset. The trial was conducted before the emergence of the Omicron variant and its subvariants. Pregnant people, lactating people, and children were excluded from the study. Participants were randomized to receive molnupiravir 800 mg PO every 12 hours for 5 days or placebo.

The primary composite outcome was all-cause hospitalization (defined as a hospital stay >24 hours) or death by Day 29. The final analysis included 1,433 participants; the median age was 43 years (with 17% aged >60 years). Forty-nine percent of the participants were men, 57% were White, 50% were Hispanic/Latinx, and 5% were Black or African American. Among the participants, 74% had a body mass index ≥30 and 16% had diabetes. The time from COVID-19 symptom onset to randomization was ≤3 days in 48% of the participants.

By Day 29, the use of molnupiravir reduced the risk of hospitalization or death by 31%, with 48 of 709 participants (6.8%) in the molnupiravir arm experiencing hospitalization or death compared with 68 of 699 participants (9.7%) in the placebo arm (-3.0% adjusted difference; 95% CI, -5.9% to -0.1%). The molnupiravir arm had 1 death, and the placebo arm had 9 deaths. There were no significant differences between the arms in the proportion of participants who experienced adverse events or serious adverse events. A secondary analysis of data from the patients who were hospitalized during the trial revealed
that the use of molnupiravir reduced the risk of requiring respiratory interventions (conventional or high-flow oxygen delivery or noninvasive or invasive mechanical ventilation) by 21%.8

References