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Molnupiravir; an effective drug in treating COVID-19?

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Key point

Developing effective antiviral drugs to treat severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection continues to be a challenge since its outbreak two years ago. Molnupiravir could be a potential therapeutic candidate to treat infected patients with SARS-CoV-2. However, there have been concerns about the possibility of molnupiravir-induced carcinogenesis and birth defects.

Keywords: Molnupiravir, SARS-CoV-2, RNA-dependent RNA polymerase

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Developing highly effective antiviral agents to treat severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection continues to be a challenge. The virus has the potential to cause critical coronavirus disease 2019 (COVID-19) infections that require long-term hospitalization. Antiviral medications are nucleoside analogs that inhibit the RNA chain elongation by targeting the viral polymerases. However, coronaviruses have an exonucleolytic proofreading activity that can remove misincorporated nucleotides from the nascent RNA 3′ end. Therefore, the chain-terminating antivirals are mostly ineffective against SARS-CoV-2 (1, 2).

Remdesivir (RDV) is an antiviral drug that inhibits the viral RNA-dependent RNA polymerase (RdRp) (3). It was the first approved treatment for SARS-CoV-2 infection by the United States Food and Drug Administration (FDA) (4). Antibody therapy has been approved for emergent outpatient treatment of individuals that are high-risk for developing a severe infection or hospitalization requirement (4,5). RDV and antibody therapies are both administered intravenously which limits their use, particularly in outpatient settings.

Molnupiravir (also known as EIDD-2801) is a new promising therapeutic candidate for COVID-19 infection. It targets the RdRp of SARS-CoV-2 and is a prodrug of the nucleoside analog β-d-*N*4-hydroxycytidine (NHC or EIDD-1931) in the isopropyl ester form (6). In addition, molnupiravir, similar to remdesivir, is known as an antiviral drug for coronaviruses. It increases the frequency of G-to-A and C-to-U transition mutations (7,8). In contrast to the antiviral nucleoside analogs, such as fluorouracil (5-FU) and ribavirin, molnupiravir is resistant to the coronavirus-encoded proofreading exoribonuclease (7,9,10). Therefore, molnupiravir seems to be a suitable therapeutic option for COVID-19 that requires further investigation.

Molnupiravir inhibits the replication of SARS-CoV-2 in human lung tissues implanted in immunodeficient mice and has shown effective prophylaxis against SARS-CoV-2 (11). Another study also reported that molnupiravir is effective in treating SARS-CoV-2-infected ferrets by reducing the viral load in the upper respiratory tract. In addition, it inhibits the transmission of SARS-CoV-2 to untreated animals that had contact with the infected animals (12).

Contrary to the currently approved therapies, such as remdesivir and monoclonal antibody which require infusion administration, molnupiravir is available orally (11). In a phase three trial, the MOVe-OUT trial (MK-4482-002) (NCT04575597) (13), molnupiravir significantly lowered the risk of hospitalization and mortality in COVID-19 patients that participated in the trial (14). Within five days of developing

symptoms, all 775 participants in the study were randomized to either receive molnupiravir or a placebo. All of the study participants were unvaccinated and had at least one risk factor for developing severe infection. Obesity, age over 60 years, and a history of diabetes or heart disease were the most prevalent risk factors. More than 170 sites carried out the phase three trial, including in the U.S. and other countries such as Brazil, Italy, South Africa, Japan, Taiwan, and Guatemala. The study found that the efficacy of molnupiravir was unaffected by the onset of symptoms or the presence of underlying risk factors in patients. Additionally, it demonstrated consistent efficacy against all SARS-CoV-2 variants including the widely prevalent and highly transmissible delta strain (14). Furthermore, according to the Merck Sharp and Dohme Company, none of the 385 individuals treated with molnupiravir died after 29 days, and only 28 participants were hospitalized. On the other hand, 53 individuals required hospitalization, and eight died in the control group of 377 participants who received a placebo (14).

Current researches have demonstrated that molnupiravir has the potential to be a leading example of an antiviral drug that is developed through lethal mutagenesis. However, this strategy may be followed by some adverse events. The ribonucleotide reductase of the host cell can convert NHC to the 20-deoxyribonucleoside form which can subsequently be integrated into the DNA of the host cell. NHC is mutagenic in animal cell cultures. This raises concerns about the possibility of molnupiravir-induced carcinogenesis. The mutagenesis of host DNA can also cause birth defects by affecting the sperm precursor cells and embryo development (15).

Authors' contribution

Both FK and AP searched the literature and prepared the first draft. SH conducted a scientific edit. HRGT and SS conducted the English edit and improved the scientific quality of the paper. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of the work.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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