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MOLNUPIRAVIR-THE NEXT WONDER DRUG ???

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INTRODUCTION

The coronavirus disease 2019 (Covid-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has seen almost 270 million confirmed cases and over 5.2 million reported deaths worldwide.[1] A substantial portion of patients with Covid-19 need hospitalization, predominantly older adults and persons with preexisting conditions (e.g., obesity, diabetes mellitus, and serious cardiac conditions).[2-4] Several vaccines that are highly effective in reducing the incidence of hospitalization and death have been authorized; however, vaccine coverage remains insufficient.[5,6] Antiviral therapies that reduce the risk of Covid-19 progression are needed. Since trials have shown the need for initiation of treatment as soon as possible after the onset of symptoms,[7-9] such therapies would ideally be readily available and easily administered by the patients themselves.[10,11]

Molnupiravir is a small-molecule ribonucleoside prodrug of N-hydroxycytidine (NHC), which has activity against SARS-CoV-2 and other RNA viruses and a high barrier to development of resistance.[12-19] After oral administration of molnupiravir, NHC circulates systemically and is phosphorylated intracellularly to NHC triphosphate. NHC triphosphate is incorporated into viral RNA by viral RNA polymerase and subsequently misdirects the viral polymerase to incorporate either guanosine or adenosine during viral replication. This leads to an accumulation of deleterious errors throughout the viral genome that ultimately render the virus noninfectious and unable to replicate.[1]

Mechanism of Action

It appears to work by the mechanism of "error catastrophe" which is essentially based on the concept that by increasing the rate of mutation in the viral genome beyond a biologically tolerable threshold it will become lethal to the virus and lead to its extinction.[5] The broad-spectrum antiviral activity of this drug is attributed to its 2-step mutagenesis mechanism. Molnupiravir is an isopropyl ester prodrug, which is cleaved in plasma by host esterases to an active nucleoside analog b-D-N4-hydroxycytidine (NHC) or EIDD-1931.[6] This active form of the drug is distributed to various tissues and subsequently converted to its corresponding 50 -triphosphate (NHC triphosphate or MTP). This then targets the RdRp which is virally encoded and competitively inhibits the cytidine and uridine triphosphates and incorporates M instead. The RdRp uses the NHC triphosphate as a substrate instead of the cytidine and uridine triphosphates and then incorporates either A or G in the RdRp active centers forming stable complexes and thus escaping proof reading by the synthesis of a mutated RNA.[7,8] Kabinger et al. confirmed with structural studies about the formation of M-G and M-A base pairs in the active center of RdRp and after cryo-EM density interpretation assumed that one stable tautomer predominates in each case, that is, aminoM tautomer forms a base pair with G and the imino-M tautomer forms a base pair with A and do not impair the RdRp progression.[6] Thus, the 2-step mutagenesis can be summarized as follows- in the first step, RdRp synthesizes negative strand genomic RNA(-gRNA) by using positive strand genomic RNA(þgRNA) as a template. Following this, in the second step, þgRNA or sub genomic RNA is synthesized using M-containing RNA as template,[10] The M containing RNA in the -gRNA causes mutation in þgRNA and subgenomic RNA subsequently formed resulting in mutagenesis which is lethal to the virus.[5,6] Fig. 1 illustrates the mechanism of action (schematic representation) of molnupiravir against SARSCoV-2 and its comparison with remdesivir and favipiravir. These mutations are also produced in the host cell (mammalian DNA) which raises concerns regarding its interference with vaccination, and its potential carcinogenic and teratogenic effects which are theoretically possible with mutagenic drugs.[9] However, it might be less likely because of its proposed short-term use e twice daily for 5 days. It is also interesting to note that RNA synthesis in hepatitis C polymerase or RNA

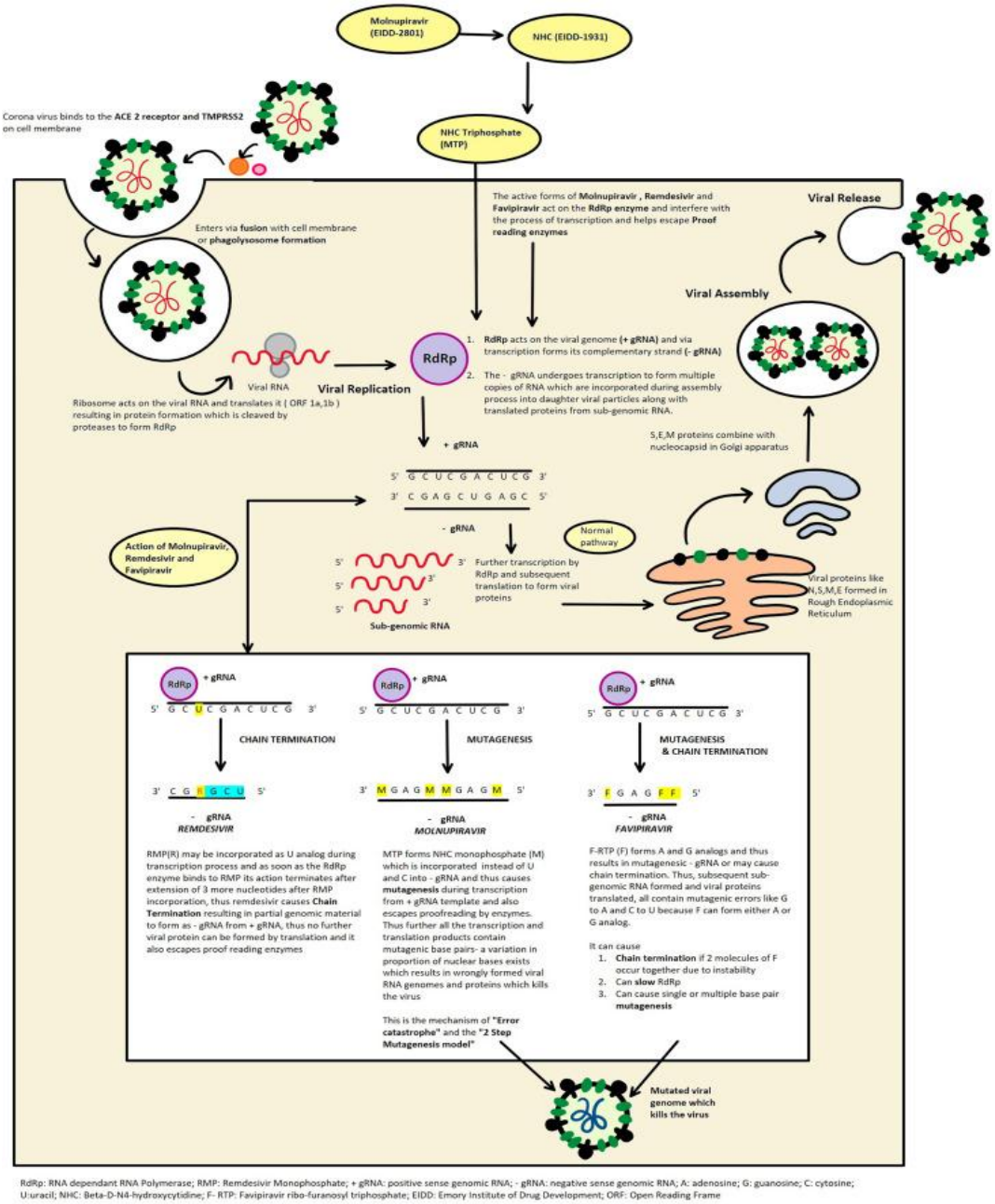
polymerase of respiratory syncytial virus is not seen with NHC triphosphate.[8]

Pharmacokinectics

After an 800 mg oral dose of molnupiravir every 12 hours, the active compound (N4-hydroxycytidine) reaches a C_{max} of 2970 ng/mL, with a T_{max} of 1.5 hours, and an $AUC_{0\text{-}12h}$ of 8360 ng/mL.[6]Molnupiravir and the active metabolite, N4-hydroxycytidine, are not protein bound in plasma.[6]

Molnupiravir is hydrolyzed to N4-hydroxycytidine, which distributes into tissues.[2] Once inside cells, N4-hydroxycytidine is phosphorylated to the 5'-triphosphate form.[2]≤3% of an oral molnupiravir dose is eliminated in the urine as the active metabolite N4-hydroxycytidine.[6]

The half life of the active metabolite, N4-hydroxycytidine, is 3.3 hours.[9]



RdRp: RNA dependant RNA Polymerase; RMP: Remdesivir Monophosphate; + gRNA: positive sense genomic RNA; - gRNA: negative sense genomic RNA; A: adenosine; G: guanosine; C: cytosine; U:uracil; NHC: Beta-D-N4-hydroxycytidine; F- RTP: Favipiravir ribo-furanosyl triphosphate; EIDD: Emory Institute of Drug Development; ORF: Open Reading Frame

Fig. 1: Mechanism of action of molunaprivir.

Recommendations

In nonhospitalized patients aged ≥18 years who have mild to moderate COVID-19 and who are at high risk of disease progression, recommends using molnupiravir 800 mg orally (PO) twice daily for 5 days only when ritonavir-boosted nirmatrelvir (Paxlovid), sotrovimab, or remdesivir cannot be used; treatment should be initiated as soon as possible and within 5 days of symptom onset.[18] There are no data on the use of molnupiravir in patients who have received COVID-19

vaccines. The risk-to-benefit ratio is likely to be less favorable in these patients, because molnupiravir has a lower efficacy compared to other available treatments.

Move- Out Clinical Trial

The primary data supporting this EUA for molnupiravir are from MOVe-OUT, a randomized, double-blind, placebo-controlled clinical trial studying molnupiravir for the treatment of non-hospitalized patients with mild to moderate COVID-19 at high risk for progression to severe COVID-19 and/or hospitalization.[19] Patients were adults 18 years of age and older with a prespecified chronic medical condition or at increased risk of SARS-CoV-2 infection for other reasons who had not received a COVID-19 vaccine. The main outcome measured in the trial was the percentage of people who were hospitalized or died due to any cause during 29 days of follow-up. Of the 709 people who received molnupiravir, 6.8% were hospitalized or died within this time period compared to 9.7% of the 699 people who received a placebo. Of the people who received molnupiravir one died during the follow-up period compared to nine people who received placebo.[19]

DOSING

800 mg orally twice daily for 5 days

Considerations In Sexually Active Individuals

Clinicians should assess a patient's pregnancy status before initiating molnupiravir, if clinically indicated.

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 receiving molnupiravir. Reproductive toxicity has been reported in animal studies of molnupiravir, and molnupiravir may be mutagenic during pregnancy.[11]

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.[13]

Considerations In Pregnancy

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 risks, particularly if they are beyond the time of embryogenesis (i.e., >10 weeks' gestation). The prescribing clinician should document that a discussion of the risks and benefits occurred, and that the patient chose this therapy. The patient should also be informed about the pregnancy surveillance program and offered the opportunity to participate.[17]

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.[15]

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 children aged <18 years due to potential effects on bone and cartilage growth.[19]

Monitoring, Adverse Effects, and 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.[14]

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