Molnupiravir and Nirmatrelvir/Ritonavir: The New Available Antiviral Options for COVID-19

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ABSTRACT

Coronavirus disease 2019 (COVID-19) is a respiratory tract disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). With the complexity of multimorbidity in Indonesia, it is crucial to find another line of antiviral for COVID-19. This article aims to review two antivirals, molnupiravir and nirmatrelvir/ritonavir, that have been studied extensively in treating COVID-19 with promising results, and their availability in Indonesia. Molnupiravir and nirmatrelvir/ritonavir are two of many repurposed drugs in clinical trials, which have been reported to have a mechanism in quick clearance of SARS-CoV-2, reduction in viral load, and fast symptoms recovery time in phase 1 and 2 clinical trials. Phase 2/3 clinical study in COVID-19 patients without any indication for hospitalization showed that molnupiravir and nirmatrelvir/ritonavir significantly reduced the risk of hospitalization and death.

Keywords**:** *antiviral, COVID-19, molnupiravir, nirmatrelvir/ritonavir, SARS-CoV-2.*

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a respiratory tract disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Up to early September 2022, the disease has caused 613 million cases and 6.5 million deaths globally.[1,2] One of the strategies in eradicating COVID-19 is vaccination, which has reached more than 12 billion doses administered worldwide.[1] Vaccination in Indonesia is underway and reaching over 204 million first dose in September 2022.[3] Although the administration of vaccine has a widespread distribution, the incidence rate of COVID-19 during this past month is still high, reaching 2,344 cases for every 100,000 people.[1,2]

In addition to vaccination as a preventive measure, proper and effective curative treatment is essential to decrease morbidity and mortality caused by COVID-19. Many studies have reported the role of COVID-19 medications, such as the use of inflammatory agents, immunoglobulin, immunomodulator, convalescent plasma, or antibiotics and antivirals. We aim to highlight the role of newly repurposed antiviral agents for COVID-19 treatment, molnupiravir and nirmatrelvir/ritonavir, which are available in Indonesia since early 2022, but have not been widely reviewed.

COVID-19 AND RNA DEPENDENT RNA POLYMERASE (RDRP)

SARS-CoV-2 is a positive single-stranded ribonucleic acid (RNA) coronavirus which is encapsulated by an envelope and a nucleocapsid.[4] It has a 29.9-kb genome with a diameter of 50-200 nm.[5] The virion has many structural proteins, i.e., spike (S), envelope (E), nucleocapsid (N) and membrane (M).[4,5] The S protein facilitates the binding of angiotensin-converting enzyme 2 (ACE2) and the host cell membrane receptor, which then helps the fusion of virus into the host cell. Inside the host cell, the replication of the viral genome occurs in cytoplasm, mediated by RNA-dependent RNA polymerase (RdRp) enzyme.[5–7]

Numerous studies have focused on RdRp as a promising therapy against viral infections.[5] RdRP is an important enzyme in majority of RNA virus' replication process. The enzyme is also relatively stable throughout the evolution of virus, does not have homologous structure in host cells, and has previously been studied. There is already adequate information on its structure and function. We will further discuss the drugs which mechanism of action are principally on the RdRp enzyme, i.e., molnupiravir and nirmatrelvir/ritonavir.

MOLNUPIRAVIR

During COVID-19, there are many preceding drugs which are repurposed as COVID-19 therapy, such as hydroxychloroquine/chloroquine, ivermectin, antibiotics, antivirals, antihypertensives, and immunomodulators. Similar to remdesivir and favipiravir, molnupiravir works as RdRP inhibitor for transcription and replication of viral RNA genome.[5,8] Molnupiravir works by the mechanism of "error catastrophe", where it increases the rate of mutation in the viral genome and eventually become lethal to the virus.[5]

Molnupiravir has a molecular formula C13H19N3O7 and its active form name is Emory Institute for Drug Development (EIDD)-1931-isopropyl ester (EIDD-1931) or β-D-N4-hydroxycytidine-5'-isopropyl ester (NHC).[5,8–11] The active form is converted to NHC-triphosphate that binds to RdRp, instead of binding to cytidine and uridine triphosphates.[12] The RdRp enzyme uses the NHC-triphosphate as a substrate and incorporates into the RdRp active centers to form stable complexes, leading to synthesis of mutated RNA. RdRp synthesizes negative strand genomic RNA (-gRNA) from positive strand genomic RNA template. The +gRNA is also synthesized from M-containing RNA. The M-containing RNA in the -gRNA causes mutation in +gRNA, and subsequently results in mutagenesis which is lethal to the virus.[11,12] The mutagenesis leads to the accumulation of deleterious errors in the genome, hence causing the inability of the virus to replicate. There is some concern that these mutations can also be produced in the host cell (mammalian DNA) and therefore, increasing its potential carcinogenic and teratogenic effects. However, the concern is less likely to happen because of molnupiravir regimens are short-term (5 days).[12,13]

The suggested dose for patients is 800 mg (with 200 mg on each tablet) orally, twice daily for five days in mild, moderate, and severe COVID-19 cases.[14] For patients with comorbidity and with risk of worsening in later stages of COVID-19, the National Institutes of Health (NIH) recommended to use molnupiravir only when nirmatrelvir/ritonavir or remdesivir cannot be used. Some of the comorbidities being studied are type I and II diabetes mellitus, malignancies, cerebrovascular diseases, chronic kidney diseases, chronic liver diseases, chronic pulmonary diseases, cardiovascular diseases, and obese population.[13,14] Molnupiravir should be started within five days of symptoms onset.[13] The contraindication of molnupiravir is pregnancy, breastfeeding, and children younger than 18 years old.[13,14] There are some exception in pregnancy, when other therapies are not available, molnupiravir can be used with risk-benefit assessment and preferably beyond 10 weeks of gestation.[13]

CLINICAL STUDIES OF MOLNUPIRAVIR

The preclinical studies of molnupiravir suggested that it has broader antiviral efficacy toward SARS-CoV-2 compared to remdesivir. A double-blind, randomized, and placebo-controlled (DBRPC) phase 1 clinical study of

molnupiravir reported that the drug is safe and most effective at the dose levels of 50-1600 mg, with half-life between 0.907 and 7.08 hours. The rate of absorption was low during meals, but with longer duration of exposure, the absorption rate of both the fed and unfed states was similar. Another phase 1 clinical study also reported safety and tolerability of 1600 mg daily dose molnupiravir up to 5.5 days, without any serious adverse events.[12] The median time needed for the active form of molnupiravir to reach maximum observed plasma concentration ranges from 1-1.75 hours. Adverse events were more prevalent in the placebo arm. In both studies, the most frequently reported adverse event was headache, without any other safety concern on vital signs, electrocardiogram data, or hematological parameters.[12]

A phase 2 clinical study of molnupiravir reported that the dose of 800 mg twice daily had good efficacy in reducing clearance time of viral RNA compared to placebo (RNA negativity), with median time of 14 days *versus* 27 days in placebo. The most common adverse events were headache, insomnia, and increased levels of alanine aminotransferase, which were reported in both molnupiravir and placebo group.[12] A phase 3 clinical study, MOVe-OUT, reported that the molnupiravir reduced the risk of hospital admission and death by 50% in mild cases of COVID-19; however, this study was criticized due to its inconsistencies in study method and result, implementation of the interim and primary analysis, significant differences between interim and post-interim results, and analysis of the result.[15,16] Bernal AJ et al also reported data from MOVe-OUT that molnupiravir group had a lower risk of hospitalization due to any cause or death until day 29 (**Table 3**). There was no significant benefit to this drug in the later stage of moderate to severe COVID-19. The efficacy of molnupiravir was not affected by the SARS-CoV-2 variant (gamma, delta, or mu), the onset time of symptoms, or the underlying risk factors.[12,16] The most common adverse events in molnupiravir group were COVID-19 pneumonia, diarrhea, bacterial pneumonia, and progressive COVID-19.[16]

A DBRPC phase 3 study (MOVe-AHEAD) is underway to evaluate the safety and efficacy of molnupiravir to prevent the incidence of COVID-19 in non-infected adults living with an infected person. There is still lack of data on molnupiravir clinical trials in vaccinated patients, but it may have lower efficacy or no benefit on this population.[13]

NIRMATRELVIR/RITONAVIR

Another repurposed drug for COVID-19 is nirmatrelvir/ritonavir, with Paxlovid™ as its brand. Unlike molnupiravir, this drug is not associated with the alarming possibilities of mutation induction in human DNA and acceleration of the development of new virus variants. Nirmatrelvir/ritonavir inhibit the main protease (M^{pro}) and 3CL protease of SARS-CoV-2.[7,17] M^{pro}, which is an attractive antiviral target because it is essential in the viral replication cycle.[17] Study of nirmatrelvir in animals had demonstrated its activity to halt the spread of COVID-19 despite the frequent mutations in the viral genomes.[7] Nirmatrelvir shows an effective antiviral effect against recent coronavirus mutants. Working in combination with nirmatrelvir, ritonavir works as a CYP3A4 inactivator and pharmacokinetic enhancer that resulted in boosting the serum concentration of nirmatrelvir. Ritonavir has also previously been used in combination with antiretroviral drugs in human immunodeficiency virus (HIV) infection.[7]

An interim result analysis of phase 2/3 clinical study EPIC-HR (Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients) stated that this drug significantly reduced the risk of hospitalization and death in COVID-19 outpatients, who have at least one comorbidity (diabetes or lung disease), with estimated risk reduction of -6.3%. During 28-day observation, 0.3% of patients in nirmatrelvir/ritonavir group were hospitalized with no mortality case, compared to 6.3% of patients in the placebo group with 12 deaths (**Table 3**).[7]

The suggested dose of nirmatrelvir for patients with normal renal function is 300 mg (with 150 mg on each tablet) and ritonavir 100 mg per tablet orally, twice daily for five days, and should be initiated within five days of symptoms onset.[18,19] The dose adjustment for moderate

renal impairment (estimated glomerular filtration rate (eGFR) ≥ 30 to ≤ 60 mL/min) is 150 mg nirmatrelvir and 100 mg ritonavir twice daily for five days. Nirmatrelvir/ritonavir is not recommended for patients with severe renal impairment (eGFR) < 30 mL/min) or with severe hepatic impairment (Child-Pugh Class C).[14,18,19]

Nirmatrelvir/ritonavir is recommended for children 12 years old and above who weigh at least 40 kg with mild to moderate COVID-19, but it is still contraindicated for children below 12 years old.[14] NIH stated that nirmatrelvir/ritonavir is safe to be used in pregnancy with risk-benefit assessment (medical comorbidities, body mass index, and vaccination status).[19] However, there is still lack of data in Indonesia regarding the safety in pregnancy, breastfeeding, and pediatric population.

Some adverse events of nirmatrelvir/ritonavir are dysgeusia, diarrhea, hypertension, and myalgia, which occur in both nirmatrelvir/ritonavir and placebo groups. The common side effects of ritonavir are nausea, vomiting, diarrhea, changes in taste, fatigue, rash, hyperlipidemia, and lipodystrophy (associated with long-term use).[7,17] The drug may also interact with antiarrhythmics (amiodarone, digoxin), oral antithrombotics (apixaban, rivaroxaban, ticagrelor), statins (atorvastatin, lovastatin, simvastatin), benzodiazepines (diazepam), opioids (methadone, fentanyl), anticonvulsants (carbamazepine), neuropsychiatric drugs, and immunosuppressants; therefore, it should be administered with caution to avoid drug interactions.[18]

WHY MOLNUPIRAVIR AND NIRMATRELVIR/RITONAVIR ESSENTIAL FOR HIGH-RISK PATIENT?

For clinical symptoms outcome, Fisher W et al reported that there are no significantly difference in patients with molnupiravir and placebo. Time to resolution of COVID-19 symptoms was not statistically different between participants.[10] Until now, there is still limited data that discuss about clinical resolutions of COVID-19 symptoms, so there is a need for more studies to learn about symptoms resolutions and preventive effect of antivirals for long COVID-19. Many of the studies have reported clinical data, such as hospitalization rate and death. Even though clinical symptoms outcome data are still lacking, Lai CC et al reported that between three antiviral agents as interventions (molnupiravir, remdesivir or nirmatrelvir/ritonavir) and placebo, with the same study design (**Table 1** and **Table 2**)[20], showed that, Nirmatrelvir/ritonavir is superior than its predecessor and molnupiravir has better outcome than placebo.

High risk patients who are recognized by MOVe-OUT study and CDC are people with >60 years of age, active cancer, chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), obesity (body mass index (BMI) ≥ 30 kg/m^2), serious heart conditions (coronary artery diseases (CAD), heart failure, cardiomyopathies), hypertension, diabetes mellitus, immunosuppressive diseases or immunosuppressive treatments, neurodevelopmental disorders (cerebral palsy) or other conditions that confer medical complexity (genetic or metabolic syndromes and severe congenital anomalies), and having a medical-related technological dependence (tracheostomy, gastrostomy).[21] Toussi SS et al reported that implementation of nirmatrelvir/ ritonavir in renal impairment needs dosage adjustment.[22] With current limitation of high-risk patients that could be included in molnupiravir and nirmatrelvir/ritonavir studies, there is already reduced risk of hospitalization and death. In future studies,

Table 1. Results of the pairwise comparisons in the network meta-analysis between antiviral agents for COVID-19.[20]

Antiviral Agents*	Nirmatrelvir Plus Ritonavir	Remdesivir	Molnupiravir	Placebo
Nirmatrelvir Plus Ritonavir		0.89 (0.17-4.69)	0.17 (0.07-0.39)	0.12 (0.06-0.24)
Remdesivir	1.12 (0.21-5.88)		0.19 (0.04-0.89)	0.13 (0.03-0.57)
Molnupiravir	5.85 (2.54-13.46)	5.22 (1.13-24.22)		0.67 (0.46-0.99)
Placebo	8.68 (4.15-18.17)	7.75 (1.76-34.22)	1.48 (1.01-2.18)	

*Odds ratio and 95% confidence interval were presented with drugs on the column as the reference

Table 2. Rank probabilities for treatment by P-score.[20]

Antiviral Agents	***p*-Score***
Nirmatrelvir + ritonavir	0.8510
Remdesivir	0.8087
Molnupiravir	0.3317
Placebo	0.0086

*Higher probability indicates better treatment for COVID-19

we hope that all of the high-risk patients can be included in studies and the effect of these antiviral agents can be more explored.

Table 3. Summary of published phase 3 clinical trials on molnupiravir and nirmatrelvir/ritonavir.

No	Author (year)	Countries	Population (n=patients)	Outcome evaluated	% of outcome in both groups (drugs vs placebo)	Comments (if any)
Molnupiravir						
1.	Fischer W, et al (2021) ClinicalTrials.gov NCT 04405570	Multicountry	N = (204)	Decrease in infectious virus isolation Time to SARS-CoV-2 clearance of viral RNA	*Infectious virus isolation Day 3 : 1.9% (1/53) vs 16.7% (9/54) (p = 0.02) Day 5 : 0% vs 11.1% (6/54) (p = 0.03) *Time to SARS-CoV-2 clearance of viral RNA 14 Days vs 27 Days (p = 0.001)	Randomized, double-blind, placebo-controlled trial
2.	Bernal AJ, et al (2021) MOVe-OUT ClinicalTrials.gov NCT 04575597	Multicountry	N = (1450)	The risk of hospitalization or death until day 29 Adverse events	*The risk of hospitalization or death until day 29 7.3% (28 of 385) vs 14.1% (53 of 377) (p = 0.001) *Adverse events (30.4%) 216 of 710 vs 33.0% (231 of 701)	Randomized, double-blind, placebo-controlled trial
3	Painter WP, et al (2021) NCT04392219	United Kingdom	N = (130)	1. Number of reported adverse events 2.To determine the safety and tolerability of single and mutiple ascending doses of molnupiravir	*Adverse events Headache (12.5% vs 18.8%) Diarrhea (7.1% vs 7.1%) *Single ascending doses Reported adverse events (43.8% vs 35.4%) *Mutiple ascending doses Reported adverse events (50% vs 42.9%)	Randomized, double-blind, placebo-controlled trial
Nirmatrelvir/Ritonavir						
1.	Hammond J, et al (2022) EPIC-HR NCT04960202	Multicountry	N = (2246)	1.The incidence of COVID-19 related hospitalization or death by day 28 2.The incidence of adverse events	*Incidence of COVID-19-related hospitalization or death by day 28 0.77% (3 of 385) vs 7.01% (27 of 385) Deaths : 0 vs 7 6.32% reduction (95% CI, -9.04 to -3.59; p<0.001; relative risk reduction, 89.1%) *Adverse events : 22.6% vs 23.9% Serious adverse events : 1.6% vs 6.6% Adverse events leading to discontinuation : 2.1% vs 4.2%	Randomized, double-blind, placebo-controlled trial

MOLNUPIRAVIR AND NIRMATRELVIR/ RITONAVIR AVAILABILITY AND USE IN INDONESIA

On the 13th of January 2022, the Indonesian National Agency of Drug and Food Control stated that the Emergency Use Authorization (EUA) of molnupiravir has been granted.[23,24] The use of molnupiravir is already registered on Indonesian National Agency of Drug and Food Control. However, nirmatrelvir/ritonavir has not been granted EUA yet in Indonesia. Regarding the availability of molnupiravir in Indonesia, through www.covid19.go.id as the official website for COVID-19 in Indonesia, the Ministry of Health of the Republic of Indonesia reported that they have prepared 400 thousand tablets for the ongoing month since 17th of January 2022. The Indonesian Medical Association, which includes the Indonesian Society of Respirology, the Indonesian Heart Association, the Indonesian Society of Internal Medicine, the Indonesian Society of Anesthesiology and Intensive Therapy, and the Indonesian Pediatric Society, has given their recommendation for use in the fourth edition of guidelines for COVID-19 treatment on January 2022.

CONCLUSION

There has been new insight on the use of antivirals for COVID-19 treatment as molnupiravir and nirmatrelvir/ritonavir has now been made available in Indonesia. Despite the rising number of people who got vaccinated, antiviral treatment is still an important aspect needed to treat COVID-19 infection. In indicated patients, molnupiravir and nirmatrelvir/ritonavir are expected to have a greater impact in the society, i.e., to reduce the risk of hospitalization and death than its predecessor antivirals and placebo. With promising results from preclinical, phase 1, phase 2, and phase 3 studies, both drugs are considered to be safe and tolerable without any serious adverse events.

CONFLICT OF INTEREST

The authors affirm no conflict of interest in this study.

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All named authors have met the criteria for authorship, took responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

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