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REVIEW ARTICLE

Efficacy and safety of Molnupiravir in COVID-19 patients: a systematic review

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Abstract

Background Molnupiravir is an oral antiviral drug that received Emergency Use Authorization in three countries for the treatment of mild COVID-19. The aim of this systematic review was to find out the safety and efficacy of Molnupiravir in SARS-COV-2 infections.

Methods The electronic databases such as PubMed, MedRxiv, BioRxiv, FDA, ClinicalTrials.Gov, ctri.nic.in and Google Scholar were searched for articles from January 2021 to March 2022 using the keywords such as "Molnupiravir", "COVID-19", "Oral antiviral pill", "MK-4482", "EIDD-280", "Efficacy" and "Safety". Details of published, unpublished with interim reports and ongoing studies of Molnupiravir in COVID-19 were retrieved, and a systematic review was performed.

Results A total of 6 articles and 18 ongoing trials data were collected. Out of these, data from 4 published and 2 unpublished with interim reports were extracted. After review of these studies, it was observed that the daily dose of 1600 mg Molnupiravir for 5 days was safe and tolerable with nausea, diarrhea and headache as the common adverse effects. The results also showed significant decrease in time to viral clearance with 800 mg twice daily in mild patients and reduction in the risk of hospitalization or death by 50% in non-hospitalized COVID-19 patients.

Conclusion Evidence from clinical studies showed that Molnupiravir caused significant reduction in the risk of hospitalization or death in high-risk mild COVID-19 patients. Molnupiravir was also found to be well tolerated and safe without any major adverse events on short-term use. For confirmative use of this drug in mild-to-moderate COVID-19 disease, further studies are required in vaccinated COVID-19 patients and against emerging variants.

Keywords COVID-19 · Emergency use authorization · Mild patients · Molnupiravir · Oral antiviral pill · SARS-COV-2

Introduction

The COVID-19 pandemic, caused by SARS-CoV-2, had resulted in significant increase in mortality and morbidity globally. The clinical profile of COVID-19 ranges from asymptomatic to life-threatening events. Early intervention in asymptomatic and mild COVID-19 patients in high-risk category would reduce the further progress of disease. When there is a high level of viral RNA in the blood, there will be more chances of severe infection, transmission and hospitalization. Therefore, an effective oral antiviral drug is required to combat this. Currently, remdesivir is the only antiviral drug that is approved by the US-FDA for the treatment of

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SARS-CoV-2 infection. Some of the antiviral drugs used off label are favipiravir, lopinavir, oseltamivir, among others. Recently, many drugs received emergency use authorization (EUA) by the US-FDA for COVID-19 including the combination of nirmatrelvir and ritonavir, Molnupiravir, and anti-SARS CoV-2 antibodies.

Molnupiravir

Molnupiravir is one of the oral antiviral drugs under consideration for COVID-19. This oral agent was developed by Drug Innovation Ventures at Emory University, Atlanta, GA and later was acquired by Ridgeback therapeutics in partnership with Merck and Co, USA. Previously, it was developed for the treatment of influenza viruses and encephalitic alpha viruses like Venezuelan, Eastern and Western equine encephalitic viruses with its significant inhibitory effect in cell cultures [1, 2].

Pharmacokinetic studies showed that the twice daily administration of Molnupiravir will provide sufficient drug concentration in the respiratory tissues [3]. The dose used was 800 mg orally twice daily for 5 days, with or without food, within 5 days of symptom onset. It is available as a 200-mg capsule [4]. The clinical trials in other viral infections showed that it was well absorbed orally, and the rate of absorption significantly decreased but not the extent of absorption when given with food. Mutagenicity, reported during the use of this drug through in vitro studies, is a major drawback for not inclusion of this drug in COVID-19 treatment guidelines [5]. The commonly observed adverse effects (AE) were nausea, diarrhea and headache. Other AEs reported were back pain, hot flushes, influenza-like syndrome, pain in extremity and rhinorrhea [4–6]. It has been reported that this drug affects cartilage and bone growth and causes fetal growth retardation in preclinical studies, hence not recommended in children and pregnant woman [4, 7].

In in vitro study, addition of Molnupiravir to human airway epithelial cell culture against SARS-CoV-2, improved the air way cell function and decreased the viral titer [8]. Molnupiravir reduced the SARS-CoV-2 replication in human lung-only mice (LoM) [9] and in the Syrian hamster model [10]. Decrease in the viral RNA load was demonstrated in in vivo studies by Abdelnabi et al. In this study, Molnupiravir was studied in combination with favipiravir [11]. Molnupiravir acts by increasing the mutation rate in the SARS-CoV-2 genome which is lethal to the virus and causes death of virus [3, 8, 12, 13]. The detailed mechanism of action of Molnupiravir in COVID-19 is depicted in Fig. 1. Based on the available data in other viral infections and preclinical studies, clinical trials were conducted with Molnupiravir for SARS-COV-2 infections.

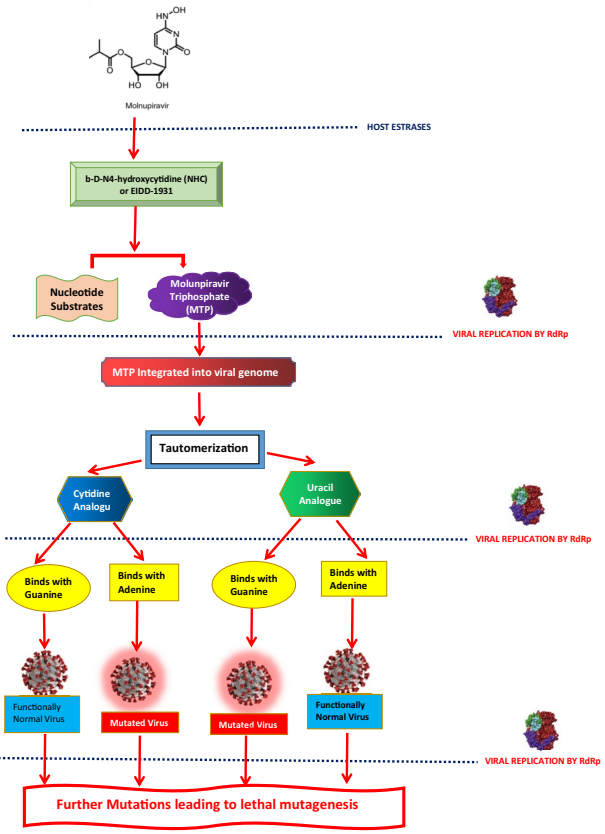

Fig. 1 Mechanism of action of Molnupiravir in COVID-19. Molnupiravir is a prodrug, converted to an active nucleoside b-D-N4-hydroxycytidine (NHC) by the host esterases present in the plasma. This active compound is converted to its triphosphate (NHC triphosphate). RNA-directed RNA polymerase (RdRp) uses NHC triphosphate as its substrate in place of cytidine and uridine forming stable complexes and forms mutated RNA. This escapes from proofreading. Molnupiravir increases the mutation rate in the viral genome which exceeds biologically tolerable threshold ("error catastrophe"). This mutation is lethal to the virus and finally leads to death of virus [12, 13]

The present systematic review was conducted with the aim to find out the evidence on efficacy and safety of Molnupiravir in COVID-19 through clinical studies.

Methods

Search strategy

Literature search was carried out by two authors (KRM and ME) in PubMed, MedRxiv, BioRxiv, FDA, ClinicalTrials.Gov, ctri.nic.in and Google Scholar and also by cross-referencing the articles. Keywords used for the purpose of this review included "Molnupiravir", "MK-4482", "Oral antiviral pill", EIDD-2801", "COVID-19", "SARS-CoV-2″, "Efficacy", "Safety" and "Clinical Trial". The literature search was

done for the articles published from January 2021 to March 2022. The search strategy is depicted in Fig. 2.

Selection criteria

Intervention studies, original research mainly Randomized Controlled Trials (RCTs) and interim reports of unpublished RCTs were included in this review.

Articles were screened by examining the titles and abstracts. Articles with inaccessible full text, preclinical studies, review and duplicated articles, commentaries, editorials, perspectives and conference papers were excluded.

An additional search was done in the ClinicalTrials.gov and ctri.nic.in for ongoing clinical trials with Molnupiravir in COVID-19. The details of the ongoing trials data was collected from CTRI India and clinical trials.gov.

Data extraction

For eligible articles, full text was accessed and read for the purpose of this review. Data extraction was done for original research studies of published and unpublished with interim reports. The data extraction sheet was used to extract details such as study title, author name, year of publication, objectives, study participants (inclusion and exclusion criteria), interventions, outcomes (both safety and efficacy).

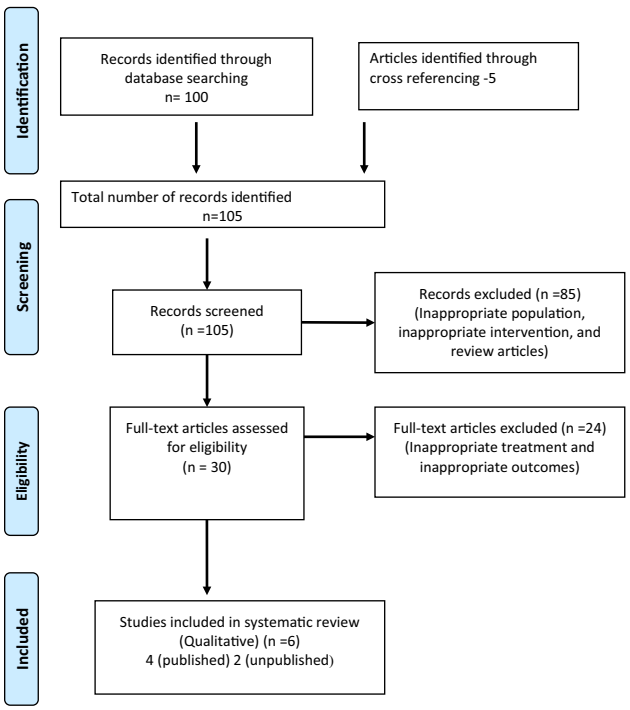

Fig. 2 PRISMA flow chart

For ongoing studies, the trial registration number, type and phase of study, sample size, arm details, inclusion and exclusion and outcomes were noted.

Outcomes

Outcome parameters to assess safety and efficacy of Molnupiravir were categorized as below:

- Efficacy
  - Incidence of hospitalization or death at day 29
  - Mean viral load
  - RT-PCR negativity
  - Isolation of infectious virus from nasopharyngeal swabs
  - Clinical improvement and progression of COVID-19
- Safety: Reported adverse events (AEs)/SAEs (serious adverse events)/death

Results

A total of 100 articles were collected. After initial screening, 30 articles were included. After full text review, 4 RCTs and 2 unpublished RCTs with interim reports were included for this review. The data of 18 ongoing trials was also collected.

Published clinical studies

Out of the 4 studies with Molnupiravir, the phase I study was done on healthy volunteers ($n = 130$) to find out the safety and dosing range of Molnupiravir. It was found safe and well tolerated. There was no decrease in absorption in the fed state. The tested dose ranges from 50 to 800 mg (single dose up to 1600 mg) two times a day for 5 and half days. The incidence of adverse events in placebo group was higher compared to Molnupiravir group; it was 43.8% vs. 35.4%, with single dose and 50.0% vs. 42.9%, multiple ascending doses, respectively (Table 1). The most commonly reported adverse event was headache in single ascending dose study and diarrhea in multiple ascending dose study [4].

The second study was AGILE trial which was a Phase Ib/IIa dose escalation study conducted in eighteen COVID-19 patients. Patients within 5 days of symptom onset were recruited and randomly allocated to three sequential dose cohorts (300, 600 and 800 mg) of 6 participants in each group. The results showed that 25% of patients who received 800 mg and 83% of standard of care had mild adverse events. Molnupiravir 800 mg twice daily was considered safe and well tolerated, with a plasma

Table 1 Safety data of Phase I and Phase II studies on Molnupiravir

Type of study	Size and type of sample	Outcome parameters	Results	Author and country
Phase I randomized, double-blind, placebo controlled study in healthy volunteers	130 healthy volunteers	i) To determine the safety and tolerability of single-dose 50 to 1600 mg M vs. P and multiple ascending doses–50 to 800 mg BID M vs. P	50 to 800 mg twice daily dose for 5 days and a single dose up to 1600 mg was found to be safe and well tolerated Single-dose AEs–35.4% vs. 43.8% (M vs. P) Multiple-dose AEs: 42.9% vs. 50% Most common AEs–headache (vs. 12.5% vs. 18.8%), diarrhea–(7.1% vs. 7.1%)	Painter et al USA and UK[4]
Phase I, open-label, randomized, controlled Bayesian adaptive trial	18 participants, 300mg ($n=4$), 600 mg ($n=4$), 800 mg ($n=4$), controls ($n=6$) Mild or moderate disease COVID-19 within 5 days of symptom onset, free of uncontrolled chronic conditions and ambulant in the community	Dose-limiting toxicity, safety, clinical progression–WHO Ordinal Scale, NEWS2 score	Well tolerated at 300, 600 and 800 mg doses with no SAEs 25% patients receiving 800 mg and 83% receiving SOC were reported to have one mild AEs Highest dose of 800 mg twice daily had a 0.9% probability of having 30% excess toxicity over the controls At day 15, all participants had a WHO Ordinal Scale score of 1 or 2 At day 15, 300 mg, 600 mg of M and controls had a median NEWS2 score of 0, while 800 mg of Molnupiravir had score of 1	Khoo et al UK [14]

NEWS2 National Early Warning Score, *SOC* standard of care, *M vs. P* Molnupiravir vs. Placebo, *AEs* adverse events

concentration within the target range [14]. Other details of Phase I and Phase II clinical trials on Molnupiravir are shown in Table 1.

The Phase IIa study was conducted in 202 unvaccinated adults with 200, 400, and 800 mg of Molnupiravir in RT-PCR positive SARS-CoV-2 infection. The baseline antibodies status was higher (35%) compared to placebo (18%) group. Results showed that the time to viral clearance was significantly decreased in the Molnupiravir 800 mg arm compared to the placebo arm (log-rank p value < 0.013, median: 14 days vs. 15 days) but not with 200 mg and 400 mg of Molnupiravir. This was highly significant in sero-negative patients (median: 14 days vs. 27 days; p value < 0.01). On day 28, the viral clearance was 92.5%, 91.3%, 78.7% and 80.3% with 800 mg, 400, 200 mg of Molnupiravir and placebo, respectively.

The isolation of virus from nasopharyngeal swabs was significantly less in Molnupiravir group compared to placebo group, and it was 1.9% vs. 16.7% and 0% vs. 11.1% on day 3 and day 5, respectively. The significant difference was observed between the doses of 400 and 800 mg of Molnupiravir.

The median time to resolution of COVID-19 symptoms was 8 days (95% CI, 6.0 to 12.0) vs. 8.5 days (95% CI, 7.0 to 11.0) in Molnupiravir 800 mg and placebo, respectively. Adverse events and other primary outcomes are mentioned in Table 2 [15].

Phase III clinical trial (MOVe-OUT trial) was conducted in non-hospitalized patients with mild-to-moderate disease and with at least one risk factor for progression to severe illness. It has been reported that, in the intention-to-treat population, the risk of hospitalization for any cause or had died through day 29 was lower with Molnupiravir (7.3% [28 of 385 participants]) compared to placebo (14.1% [53 of 377 participants]). The difference reported was −6.8 percentage (95% confidence interval [CI], −11.3 to −2.4; $p = 0.001$). The absolute risk difference of −5.4 (95% confidence interval, −9.9, −1.0) was observed on high viral load (> 10^6 copies/mL) at baseline.

A pre-specified supporting analysis showed that only 6.3% vs 9.2% of COVID-19–related hospitalizations or deaths occurred in the Molnupiravir group compared to the placebo group (difference, −2.8 percentage points; 95% CI, −5.7 to 0.0).

One death was reported in the Molnupiravir group, and 9 were reported in the placebo group through day 29. Adverse events were reported in 216 of 710 participants in the Molnupiravir group and 231 of 701 in the placebo group. At baseline, quantifiable RNA was confirmed in 77.6% nasopharyngeal samples. The mean change of SARS-CoV-2 nasopharyngeal RNA titer from baseline over time was −0.33 (95% CI, −0.50, −0.16) [16].The efficacy and safety outcome details are shown in Table 2.

Unpublished studies with interim reports

The unpublished studies whose interim reports/data were given in the press release have been summarized in Table 3. These studies were Phase III studies conducted by Hetero Pharma [17] and Optimus Pharma companies [18] in India. For review of the data, the information was obtained from the press release information by Hetero Pharma Company and through email communication from the Optimus Pharma Company. Incidence of hospitalization was very less on day 14 in Phase III conducted Optimus Pharma. The clinical improvement based on a 2-point decrease in WHO clinical progression scale was significant on day 5, and the difference was nearly 40% in the Hetero Pharma study and not significant in the Optimus Pharma trial. Significantly increased RT-PCR negativity was observed from Day 5 to Day 14 in case of Hetero Pharma trial results and Day 5 to Day 10 in Optimus Pharma trial. Median time to clinical improvement was significantly reduced in the Hetero Pharma trial but not in the Optimus Pharma trial. Discontinuation of treatment due to drug-related AEs was reported in around 0.3% in the Optimus Pharma trial.

Ongoing clinical trials

There are nearly 18 ongoing trials with Molnupiravir registered with CTRI and clinicaltrial.gov. In these trials, Molnupiravir at 800 mg twice daily plus standard of care is comparing with standard of care alone. Most of the studies are testing this drug in mild COVID-19 patients. Six trials are registered in clinical trials.gov and remaining in CTRI India. Four studies are testing Molnupiravir in moderate cases of COVID-19. One trial (MOVe-AHEAD) is being conducted in the prevention of COVID-19. Details of the sample size and outcome parameters to be measured are shown in Table 4 [19–23].

Approval status by regulatory authorities of various countries

Medicines and Healthcare products Regulatory Agency (MHRA) of the UK authorized Molnupiravir on November 4, 2021, based on interim analysis of MOVe-OUT study. Molnupiravir from Ridgeback/Merck had received EUA by the US-FDA on December 23, 2021 for non-hospitalized adult patients with mild-to-moderate COVID-19. Additionally, Molnupiravir had also received restricted use authorization (RUA) from the Central Drugs Standard Control Organization (CDSCO), India on December 28, 2021 [24].

Table 2 Efficacy and safety outcomes of published studies on Molnupiravir in COVID-19

	Study 1 (Phase IIa)	Study 2 (Phase III)
Author and country	Fischer, USA[15]	Jayk Bernal, Brazil[16]
Study design	Randomized placebo-controlled trial	Randomized placebo-controlled trial
Age in years	42 vs. 39.0	42.0 vs. 44.0
Male/female	50.9 vs. 49.1 (M) 45.2 vs. 54.8 (P)	46.4% vs. 53.6% 51% vs. 49%
Method of randomization	3:1 for 800 mg by using REDCap randomization application	Stratified–block of four
Sample size M vs Placebo	202 200 mg ($n=23$), 400 mg ($n=62$), 800 mg ($n=55$), Placebo ($n=62$)	1433 (716 vs. 717)
Dose	200 mg, 400 mg, 800 mg BID/5 days	800 mg BID for 5 days
At least one risk factor	60% vs. 59.7%	99.4 vs. 99.3
Type of participants	Unvaccinated adults aged ≥ 18 years, positive test for SARS-CoV-2 infection within 96 h and had onset of symptoms of COVID-19 within 7 days at the time of treatment initiation	Mild-to-moderate disease, non-hospitalized, unvaccinated and at least one risk factor for progression to severe illness (age > 60 years, obesity, diabetes or cardiovascular disease)
Duration of follow-up	28 days	29 days
Baseline SRAS Cov-2 spike Ab	With 800 mg 35.3% vs. 18.1%	19.1% vs. 20.5%
Outcomes		
Incidence of hospitalization or death at day 29	8.6% vs. 8.1%	6.8% vs. 9.7%
Mean viral load (M vs P)- ($\log_{10}$ copies/mL) Day 5 end of treatment	0.129 vs. 0.150 (least square means)	2.91 vs. 2.92
Median time to viral clearance (in Days M −800 mg vs P)	14 vs. 15 days overall 14 vs. 27 in sero-negative; $p<0.01$	-
Proportion of participants who achieved SARS-CoV-2 RNA clearance by day 28 (end of study)	92.5% vs. 80.3%	-
Safety		
With one adverse event	20% vs. 29%	30.4% vs. 33%
Death	-	0.1% vs. 1.7%
COVID-19 pneumonia	-	6.3% vs. 9.6%
Diarrhea	0 vs. 1.6%	2.3% vs. 3.0%,
Bacterial pneumonia		2.0% vs. 1.6%
Insomnia	1.8 vs. 6.5	0%
Discontinuation of treatment due to AEs	1.8 vs. 1.6%	2.7% vs.5.2%
SAEs	1.8% vs 1.6%	6.9% vs. 9.6%

M vs. P Molnupiravir vs. Placebo, *AEs* adverse events, *SAEs* serious adverse events

Discussion

Globally 575,887,049 confirmed cases of COVID-19 including 6,398,412 deaths have been reported to WHO as of 2 August 2022 [25]. Infection with SARS-CoV-2 virus can cause a range of clinical manifestations, from no symptoms to critical illness. Based on the severity of illness, they grouped into asymptomatic, mild, moderate and severe illness. It has been reported that mild COVID-19 disease patients with underlying co-morbidities are at high risk for progressing to severe COVID-19 [26].

A comparative risk analysis study from USA reported that nearly two-thirds of COVID-19 hospitalizations could be ascribed to diabetes, obesity, hypertension and heart failure [27].

For these high-risk people to treat mild to moderate COVID-19, US-FDA has authorized antiviral medications such as Nirmatrelvir with Ritonavir combination, Molnupiravir and monoclonal antibodies (Ab) such as Cock tail Ab, bemlaninivimab, and etesivimab and bebtelovimab.

Molnupiravir, a direct oral antiviral drug, was initially developed for the treatment of influenza viral infection.

Table 3 Efficacy and safety outcomes of Molnupiravir in COVID-19 unpublished studies

Organization/author	**Hetero, Pharma, India**[17] Interim report	**Optimus Pharma, India**[18]
Type of patients	Mild COVID-19 cases	Mild COVID-19 cases
Study design	Phase-III, comparative, randomized, open label trial	Phase-III, comparative, randomized, open label trial
Sample size	741 for interim analysis	$N=1202$ (M 603 vs. 599 SOC)
Dose and comparator	MOLNU 800 mg BID + SOC vs. SOC	MOLNU 800 mg BID + SOC vs. SOC
Duration of study	28 days	28 days
Outcomes		
Incidence of hospitalization at day		
14 (M + SOC vs. SOC)	1.9% vs. 6.2%	0.17% vs. 0.67%
Clinical improvement (M + SOC vs. SOC)		
1-point decrease in WHO Clinical Progression Scale		
Day 5	-	79.0% vs. 60.9% ($p<0.0001$)
Day 10	-	97.8% vs. 82.3% ($p=0.0003$)
Day 14	-	98% vs. 98.5% ($p=0.5265$)
Day 28	-	98.55 vs. 98.8% ($p=0.6338$)
Clinical improvement (M + SOC vs. SOC) 2-point decrease in WHO Clinical Progression Scale		
Day 5	63.4% vs.22.3%$p<0.0001$)	28.6% vs. 25.6% ($p=0.2459$)
Day 10	78.9% vs.49.4%($p<0.0001$	49.0% vs. 44.1% ($p=0.0897$)
Day 14	81.5% vs. 73.2% ($p<0.02$)	49.8% vs. 56.2% ($p=0.0249$)
Day 28	Not available	52.2% vs. 59.0% ($p=0.0185$)
RTPCR negativity (M + SOC vs. SOC)		
Day 5	77.3% vs.26.0%($p<0.0001$)	71.1% vs. 51.4% ($p<0.0001$)
Day 10	94.0% vs. 57.2% ($p<0.0001$)	97.8% vs. 84.6% ($p<0.0001$)
Day 14	97.0% vs. 85.2% ($p<0.0001$)	98.8% vs. 98.8% ($p=0.9773$)
Median time to clinical improvement		
(M + SOC vs. SOC)	8 vs. 12 days (p = 0.0001)	5 vs. 5
Safety		
AEs	NA	4.8% vs. 6.4%
Discontinuation of treatment	0%	0.3% vs. 0%

M Molnupiravir, *SOC* standard of care, *AEs* adverse events, *RT-PCR* reverse transcription–polymerase chain reaction, *P* placebo, *BID* twice daily, *NA* not available

This drug has shown potent antiviral activity against SARS-CoV-2. Antiviral drugs could be used to keep viral burden down in order to minimize transmission and to suppress the development of more virulent strains. Molnupiravir has received EUA in 3 countries for treatment of mild-moderate COVID-19 in certain adults who are at high risk for progression to severe COVID-19, including hospitalization or death.

It is the first oral antiviral drug to be included in the WHO treatment guidelines for COVID-19. WHO recommended this drug based on the largest data of six randomized controlled trials involving 4796 patients [28].

Molnupiravir is available as oral tablet, and four tablets (total 800 mg) should be given twice daily for 5 days within 5 days of symptom onset. It has been reported that use of this drug as early as possible after infection can help prevent hospitalization.

The NIH COVID-19 treatment guideline panel recommends use of Molnupiravir ONLY when ritonavir-boosted nirmatrelvir or remdesivir cannot be used [29].

Till now, there is no data available on the Molnupiravir combination with antiviral drugs for the treatment of mild COVID-19 patients, and further studies are required to find out if combination therapy will have beneficial effects.

Molnupiravir acts through inhibition of RdRp enzyme (RNA replicase). This enzyme catalyzes the replication of RNA from an RNA template and is one of the 16 non-structural proteins (nsp) coded by the gene. Other antivirals which inhibit this enzyme are ribavarin, sofosbuvir, remdesivir and favipiravir. The last two drugs were repurposed in COVID-19. Remdesivir has already received approval by the US-FDA for use in hospitalized COVID-19 patients. This drug is given through the parenteral

Table 4 Ongoing clinical trials with Molnupiravir in COVID-19

CTRI identifier	Type and phase of study	Type of participants	Sample size	Observation parameters
NCT04575597[22]	Efficacy and safety of Molnupiravir (MK-4482) in non-hospitalized adult participants with COVID-19 (MK-4482–002)	Non-hospitalized adults with COVID-19	1850	Percentage of participants who are hospitalized and/or die Percentage of participants with an adverse event (AE) Percentage of participants who discontinued study intervention due to an AE
NCT04746183[19]	AGILE (early phase platform trial for COVID-19)	Adults with COVID-19	600	Phase wise study
NCT05195060[20]	TURN-COVID biobank: the Dutch cohort study for the evaluation of the use of neutralizing monoclonal antibodies and other antiviral agents Against SARS-CoV-2 (TURN-COVID)	COVID-19 patient	1000	Therapeutic effect of treatment with antiviral agents at day 90 Incidence of treatment-emergent adverse events Cost-effectiveness of treatment
NCT04381936[21]	Randomized evaluation of COVID-19 therapy (recovery)	Mild COVID-19	Not specified for Molnupiravir arm	All-cause mortality on day 28 Duration of hospital stay Composite end point of death or need for mechanical ventilation
NCT04405739, ENDCOVID[22]	Phase II Double-blind randomized placebo control	Mild to moderate Hospitalized	96	i) Virological clearance ii)Incidence of AE and SAEs
NCT04939428, MOVe-AHEAD[22]	Study of MK-4482 for prevention of coronavirus disease 2019 (COVID-19) in adults (MK-4482–013)	Non-COVID residing with COVID-19 pt	1500	Percent of participants who have undetectable SARS-CoV-2 at baseline and develop COVID-19 through day 14 Percent of participants with ≥ 1 adverse event
CTRI/2021/07/034588[23]	Study to evaluate the efficacy and safety of Molnupiravir capsules when administered along with standard of care compared to standard of care alone in Indian patients with mild COVID-19 disease	Mild COVID -19 Mild cases	1220	Rate of hospitalization from randomization up to day 14 Proportion of clinical improvement at day 10, 14 and 28 Rate of hospitalization up to day 28
CTRI/2021/05/033693[23]	A prospective, randomized, parallel, multicentric, Phase III clinical trial of Molnupiravir 800 mg capsules and standard of care (SOC) compared to standard of care only in confirmed RT-PCR positive patients with mild COVID-19		1218	Rate of hospitalization on day 14 Proportion of clinical improvement at day 10, 14 and 28 Rate of hospitalization up to day 28 Mortality rate at day 14 RT-PCR negativity at day 10 and day 15 Time to clinical improvement at day14 Incidence of severity of TEAEs
CTRI/2021/05/033904[23]	To evaluate the efficacy and safety of molnupiravir capsule in treatment of subjects with mild corona virus disease (COVID-19)		1218	Rate of hospitalization from randomization up to day 14 Proportion of clinical improvement at day 10, 14 and 28

Table 4 (continued)

CTRI identifier	Type and phase of study	Type of participants	Sample size	Observation parameters
				Rate of hospitalization up to day 28 Time to clinical improvement at day14 Change in viral load up to EOT (end of treatment) Incidence of severity of TEAEs
CTRI/2021/06/034130[23]	A Phase III clinical trial to understand the efficacy and safety of Molnupiravir 800 mg in the treatment of patients diagnosed with mild COVID-19		1218	Rate of hospitalization from randomization up to day 14 Proportion of clinical improvement at day 10, 14 and 28 Rate of hospitalization up to day 28 Mortality rate at day 14 and day 28 Time to clinical improvement at day 14 Change in the score of St. Georges' Respiratory Questionnaire and WHO 11 point scale from baseline to EOT visit
CTRI/2021/06/033938[23]	This study is to evaluate benefit of adding Molnupiravir over standard treatments in mild COVID-19 subjects		1218	Rate of hospitalization from randomization up to day 14 Proportion of clinical improvement at day 10, 14 and 28 Rate of hospitalization up to day 28 Mortality rate at day 14 and day 28 Time to clinical improvement up to day 14 Rate of viral negativity at day 10, day 15 and day 28 Incidence of severity of TEAEs
CTRI/2021/06/034015[23]	A clinical study with Molnupiravir capsules 800 mg in COVID-19 patients with mild symptoms		1220	Rate of hospitalization from randomization up to day 14 Proportion of clinical improvement at day 10, 14 and 28 Rate of hospitalization up to day 28 Mortality rate at day 14 and day 28 Time to clinical improvement up to day 14
CTRI/2021/05/033739[23]	A clinical study to test the use of capsule Molnupiravir in COVID-19 patients with mild symptoms and without lung involvement		1218	Rate of hospitalization up to day 14 Proportion of clinical improvement at EOT day 10 and 14 Rate of hospitalization up to day 28 Time to clinical improvement at day 14 Incidence of severity of TEAEs Change in viral load up to EOT (end of treatment)

Table 4 (continued)

CTRI identifier	Type and phase of study	Type of participants	Sample size	Observation parameters
CTRI/2021/06/033992[23]	A clinical study to estimate the efficacy and safety of formulation of Molnupiravir in patients with mild COVID-19 infection		1218	Rate of hospitalization up to day 14 RTPCR on day 5 Post treatment follow-up day 10, 14 and 28 Rate of hospitalization up to day 28 Proportion of clinical improvement at EOT at day 10 and 14 Time to clinical improvement up to day 14 Mortality rate at day 14 and 28 Rate of viral negativity at the end of treatment, day 10 and 15 Change in viral load from baseline up to EOT (end of treatment) Incidence and severity of TEAEs
CTRI/2021/05/033864[23]	Clinical trial to evaluate the efficacy and safety of Molnupiravir capsule in treatment of subjects with moderate coronavirus disease (COVID-19)	Moderate cases	1282	Proportion of patient with clinical improvement at day 14 Proportion of patient with clinical improvement at day 28 Mortality rate at day 28 Rate of RT-PCR negativity at the end of treatment, day 14 and 28 Change in viral load from baseline up to EOT-day 14 and 28 Incidence of TEAEs (clinical and laboratory) at all visit
CTRI/2021/08/035424[23]	Study to evaluate the efficacy and safety of Molnupiravir capsules compared with Standard of Care Medications Care alone in patients who are suffering with moderate COVID-19 disease		100	Rate of hospitalization up to day 14 Proportion of clinical improvement up to day 28 Time to clinical improvement up to day 28 Mortality rate at day 28 Rate of viral negativity at the end of treatment, day 14 and 28 Change in viral load from baseline up to EOT (end of treatment), at day 14 and 28
CTRI/2021/06/034220 [23]	A Phase II/III clinical trial to understand the efficacy and safety of Molnupiravir 800 mg in the treatment of patients diagnosed with moderate COVID-19		1282	Proportion of clinical improvement at day 14 Proportion and time to clinical improvement at day 28 Mortality rate at day 28 Viral load at day 10, day 14 and day 28 Change in the score of St. Georges' Respiratory Questionnaire from baseline to EOT visit

Table 4 (continued)

CTRI identifier	Type and phase of study	Type of participants	Sample size	Observation parameters
CTRI/2021/05/033736[23]	A clinical study to test the use of capsule Molnupiravir in adult patients with COVID 19 with lung involvement		1282	Proportion of clinical improvement at day 14 Proportion of clinical improvement at day 28 Mortality rate at day 28 Viral negativity at day 10, 14 and 28 Incidence of severity of TEAEs at all visit Patients discontinued the study drug due to adverse events at all visit

TEAEs treatment emergent adverse events, *AE* adverse events, *SAE* serious adverse event, *EOT* end of treatment

route. The oral antiviral drug which gained popularity during the first wave of COVID-19 was favipiravir; however, it was not approved by US-FDA. The various features of these antiviral drugs are mentioned in Table 5.

The main concern of Molnupiravir is mutagenicity which is more closely explained with the drug's basic mechanism of action against COVID-19. Molnupiravir is a cytidine nucleoside analogue and enters the virus RNA and causes mutations that prevent it from replication. It has been reported through animal cell culture that Molnupiravir causes mutations in human DNA.

Merck has conducted assays such as Big Blue and PIG-a for assessing the mutagenicity or genotoxicity of Molnupiravir in in vivo mammalian systems. Molnupiravir, at higher and longer doses (mg/kg), gave equivocal results in in vivo PIG-a mutagenicity assay and negative results in in vivo Big Blue model [30, 31].

FDA reviewed the genotoxicity and clinical study (treatment with Molnupiravir for 5-day) data and concluded that Molnupiravir has a low risk for genotoxicity [32].

Because of the safety concern, ICMR had not included this drug in the national COVID-19 treatment protocol in spite of its approval by CDSCO under restricted emergency use category.

From the phase I and II trials, it was reported that Molnupiravir (800 mg) was safe and well tolerated with no s erious adverse events. The MOVe-OUT was a large multicentric Phase 3 clinical trial conducted in 1433 mild COVID-19 patients who are at high risk for progression to severe disease. The incidence of hospitalization is lower in the Molnupiravir-treated group, and on average it was 8% from the published reports.

During the pandemic, many drugs failed to show response against COVID-19, but Molnupiravir showed good results by decreasing hospitalization; hence, researchers considered this drug as magic pill.

The other oral antiviral drug Paxlovid, a combination of nirmatrelvir and ritonavir, has received EUA by US-FDA at the same time of Molnupiravir approval. This is based on the clinical trial conducted on 2246 participants who are at risk of progression to severe disease. When this drug was administered within 3 days of symptom onset, the incidence of COVID-19–related hospitalization or death by day 28 was 0.72% and 6.45% in nirmatrelvir group and placebo group, respectively. The difference −5.81% (95% CI, −7.78 to −3.84) was statistically significant ($p < 0.001$), and 88.9% relative risk reduction was recorded during the study. There were no deaths in nirmatrelvir group compared to 9 deaths in placebo group [33].

The above results showed the higher efficacy of nirmatrelvir and ritonavir combination compared to Molnupiravir.

Even with the indication, duration of treatment is same for both drugs; the disadvantage of Molnupiravir is that it

Table 5 Comparison of pharmacokinetics and pharmacodynamics of various antiviral drugs

	Molnupiravir	**Remdevisir**	**Favipiravir**	**Paxlovid (nirmatrelvir/ritonavir)**
Category	Antiviral	Antiviral	Antiviral	Antiviral
Company	Merck and Ridgeback's	Gilead Sciences	Fujifilm Toyama Chemical Co., Ltd Glenmark in India	Pfizer
Approval status for COVID-19	EUA	Approved by US-FDA	Approved by the National Medical Products Administration of China, the Russian Health Ministry, not by the US-FDA	EUA by US-FDA
Route of administration	Oral	Parenteral	Oral	Oral
Dose	800 mg BID for 5 days	100 mg OD for 5 days	Day 1: 1600 mg twice daily; Days 2–5: 600 mg twice daily	300 mg nirmatrelvir (two 150 mg tablets) plus 100 mg ritonavir (one 100 mg tablet) BID for 5 days
Active/prodrug	Prodrug	Prodrug	Prodrug	Active
Analogue of	Cytidine nucleotide analogue	Adenosine nucleotide analogue	Guanosine nucleotide analogue	-
MOA	Inhibition of RdRp	Inhibition of RdRp	Inhibition of RdRp	Protease inhibition
Type of COVID-19	Mild to moderate COVID-19 non-hospitalized–high-risk patients	Moderate to severe-hospitalized	Mild to moderate COVID-19	Mild to moderate COVID-19 (hospitalized–high-risk patients)
ADR	Diarrhea and headache affect cartilage and bone growth	Liver toxicity, nephrotoxicity, diarrhea	Hyperuricemia, diarrhea, liver toxicity	Dysgeusia, diarrhea, and vomiting
Important trials conducted	MOVe-OUT study	RECOVERY	Shinkai et al. [35] Ivashchenko et al. [36]	EPIC-HR trial (evaluation of protease inhibition for COVID-19 in high-risk patients)
Disadvantages	Safety issues	Parenteral and costly	Pill burden	Drug interactions

should be given as 4 tablets twice daily compared to 3 tablets twice daily with Paxlovid (Table 5).

The adverse events reported in the published studies were around 30%, but the interim analysis of the studies conducted by Hetero and Optimus Pharma showed very less (4–6%) adverse events. Commonly reported adverse events of Molnupiravir were headache, dizziness and GI symptoms.

The results of 12 ongoing trials in India will help to make appropriate decisions on Molnupiravir use in COVID-19. Only one prophylactic study is ongoing, and results of this first prevention trial of Molnupiravir (move-Ahead trial) are much awaited.

Recent systematic review and meta-analysis by Kamal L et al. reported that evidence available from preclinical and clinical studies confirms the efficacy and safety of Molnupiravir as an antiviral therapy to treat mild-to-moderate COVID-19 infections in high-risk patients. [34]

Both the published RCTs were conducted in non-vaccinated participants. At present, no data is available for use of Molnupiravir in vaccinated patients. This data is vital as a good proportion of population worldwide is currently vaccinated. Further, there are no studies on the role of Molnupiravir in breakthrough infections following vaccination.

The important challenges with Molnupiravir use in COVID-19 are as follows:

1. Mutagenicity reported in preclinical studies and long-term safety
2. Use of this drug within 5 days from symptom onset
3. Role in asymptomatic patients–when to start treatment?
4. Role of this drug in vaccinated COVID-19 patients
5. Role in immune compromised patients
6. Cost and accessibility
7. Interaction with co-administered specific anti-SARS-CoV-2 drugs
8. Comparative effectiveness and safety with other oral antivirals (like nirmatrelvir + ritonavir [Paxlovid])
9. Medication adherence (compliance)–considering the faster and less eventful convalescence occurring currently
10. Antiviral resistance–particularly with the novel strains

Conclusion

From the available evidence from clinical studies, it can be concluded that Molnupiravir at 800 mg twice daily for 5 days within 5 days of symptom onset is safe and effective in high-risk patients with mild-to-moderate COVID-19 infection. It delays the disease progression by reducing hospitalization and/or death.

The previous studies were conducted in unvaccinated patients. Presently, most of the mild cases of COVID-19 are self-limiting who generally recover uneventfully without any specific COVID-19 treatment.

For confirmative use of this drug in mild-to-moderate COVID-19 disease, further studies are required in vaccinated COVID-19 patients and in patients with various emerging SARS-CoV-2 variants and studies on comparative effectiveness with other antiviral drugs.

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Declarations

Ethics approval Not applicable (review article).

Consent to participate Not applicable.

Conflict of interest The authors declare no competing interests.

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