Journal of Pharmaceutical Care
jpc.tums.ac.ir

Safety and Effectiveness of Molnupiravir in Covid-19 Treatment: A Rapid Review

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Received: 2022-05-14, Revised: 2022-07-09, Accepted: 2022-07-13, Published: 2022-09-30

ARTICLE INFO

Article type:
Review article

Keywords:
Molnupiravir;
Covid-19;
Review

ABSTRACT

In the first stage of viral replication, Covid-19 may cause a remarkable inflammatory response in patients. Molnupiravir is an oral antiviral medicine which functions through inhibiting the viral replication of RNA viruses including Corona virus (SARS-CoV-2). The present study intends to help the policymakers decide on using of this medication in Iran.

This study is conducted on Jan. 22, 2022 (from Jan. 2014 -the year of molnupiravir production for treatment of RNA virus diseases), using a rapid review of evidence as well as reviewing reliable databases including the Cochrane library, PubMed and Google scholar. The inclusion criteria were the randomized controlled trials that investigated the safety and efficacy of Molnupiravir at different doses in patients with Covid-19, comparing with placebo or other routine care methods (Population: Covid-19 patients, Intervention: molnupiravir, Control: placebo or other routine care methods, Outcome: Safety, Efficacy and Economic status, Study design: the randomized controlled trials or HTA reports). Prescription for oral administration in 800 mg dose twice daily for 5 days to inpatients and outpatients with mild, moderate or severe symptoms in the early stages of the disease (viral phase) had the most desirable level of efficacy. This medicine has no serious side effects; since the mutations caused by this medication have not been clarified yet, it is not recommended during pregnancy and/or for women planning to become pregnant. According to the manufacturing company, in the United States, each drug package is priced at $712 for a 5-day treatment period. Molnupiravir can be used in outpatients and inpatients (Over 18 years old) with moderate or severe symptoms in the early stages of the disease. But it is not recommended during pregnancy and/or for women planning to become pregnant.

J Pharm Care 2022; 10(3): 146-150.

► **Please cite this paper as:**
Mobinizadeh M, Akbarisari A, Olyaeemanesh A, Mohammadshahi M, Ahmadnezhad E, Aboee P, et al. Safety and Effectiveness of Molnupiravir in Covid-19 Treatment: A Rapid Review. J Pharm Care 2022; 10(3): 146-150.

Introduction

Corona viruses are a large family of viruses that range from the common cold virus to the ones causing more severe diseases such as SARS, MERS and Covid-19. So far, seven human-transmitted coronaviruses have been discovered, the latest one is the Severe Respiratory Coronavirus Syndrome. The first case of Corona disease was reported in December 2019 in Wuhan, China (1).

So far, different medicines have been suggested for Covid-19 treatment, among which Molnupiravir (development codes MK-4482 and EIDD-2801) is an oral antiviral medicine which functions through inhibiting the viral replication of RNA viruses including Corona virus (SARS-CoV-2), using the "Copy Error" technique. Molnupiravir is the same Remdesivir viral enzyme for oral intake (2).

The aim of this study was review and evaluates the available evidence for the safety and efficacy of Molnupiravir in treatment of Covid-19 disease.

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Methods

This study was a rapid review of evidence which was conducted in four stages:

1) Searching the medical databases on Cochrane library, PubMed and Google scholar using a proper approach of searching keywords.
2) Screening the retrieved papers by identifying appropriate inclusion and exclusion criteria
3) Extracting data from studies using a self-made data extraction form
4) Analyzing data thematically

The research inclusion criteria were the randomized clinical trial studies that investigated the safety and efficacy of Molnupiravir at different doses in the population of patients with Covid-19, comparing with placebo or other routine care methods. The clinical trial findings were completed by health technology horizontal studies and other published reports in this field.

Results

Through searching the mentioned databases on January 30, 2022, nine articles were found that met the inclusion and exclusion criteria, three randomized controlled trials (two peer-reviews and one preprint), two health technology assessment reports and a rapid response study were selected to be used in this study. Also, by searching the clinical trials website (www.clinicaltrials.gov), seven registered clinical trials and one cohort observational study were found (Table 2).

In order to identify the recruiting local clinical trials, the website of (www.irct.ir) was also searched and one relevant study was found in this regard (Table 3).

Also, there was a news report addressing the prediction of Molnupiravir efficacy on Coivd-19 treatment in its "Possible predictions" and their results need to be confirmed by further studies in the future.

Table 1. Included Studies

Article	Year of Publication	Type	Reference
EUnetHTA Rolling Collaborative Review (RCR19) Authoring Team. Molnupiravir for the treatment of COVID-19. Diemen (The Netherlands): EUnetHTA; 2021. [date of citation]. 25 pages. Report No.: RCR19, v6.0. Available from: https //www.eunethta.eu.	May. 17, 2021	HTA Technical Report	2
AIHTA Policy Brief NR.: 002_V9 2020: Covid-19, HSS/ Horizon Scanning, Living Document December 2020. Wien: HTA Austria- Austrian Institute for Health Technology Assessment GmbH	Dec. 2020	HTA Technical Report	3
Molnupiravir, an Oral Antiviral Treatment for COVID-19	Preprint	Randomized Controlled Trial	4
Optimal dose and safety of Molnupiravir in patients with early SARS-CoV-2: a phase 1, dose-escalating, randomized controlled study	Dec. 2021	Randomized Controlled Trial	5
Molnupiravir for Oral Treatment of Covid-19 in Non-hospitalized Patients	Dec. 16, 2021	Randomized Controlled Trial	6
Should Molnupiravir be used to treat COVID-19?	Dec. 20, 2021	Rapid response report	7

Table 2. Ongoing Clinical Trial Studies related to Molnupiravir (www.clinicaltrial.gov).

No.	Title	Disease	Comparing Group	Place	Last Status
1	Efficacy and Safety of Molnupiravir (MK-4482) in Hospitalized Adult Participants With COVID-19 (MK-4482-001)	*Covid-19*	*Placebo*	*USA*	Terminated
2	Efficacy and Safety of Molnupiravir (MK-4482) in Non-Hospitalized Adult Participants With COVID-19 (MK-4482-002)	*Covid-19*	*Placebo*	*USA*	Active, not recruiting
3	Study of MK-4482 for Prevention of Coronavirus Disease 2019 (COVID-19) in Adults (MK-4482-013)	*Covid-19*	*Placebo*	*USA*	Recruiting
4	The Safety of Molnupiravir (EIDD-2801) and Its Effect on Viral Shedding of SARS-CoV-2 (END-COVID)	*Covid-19*	*Placebo*	*USA*	Recruiting
5	AGILE (Early Phase Platform Trial for COVID-19)	*Covid-19*	*Placebo and Nitazoxanide*	*South Africa-UK*	Recruiting
6	A Safety, Tolerability and Efficacy of Molnupiravir (EIDD-2801) to Eliminate Infectious Virus Detection in Persons With COVID-19	*Covid-19*	*Placebo*	*USA*	Completed
7	COVID-19 First In Human Study to Evaluate Safety, Tolerability, and Pharmacokinetics of EIDD-2801 in Healthy Volunteers	*Covid-19*	*Placebo*	*UK*	Completed
8	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	*Covid-19*	**)Casirivimab with Imdevimab* **)Sotrovimab*	*The Netherlands*	Recruiting (Cohort)

Table 3. Local clinical trials (www.irct.ir).

Title	Comparing Group	Country
Evaluation of the Efficacy of Molnupiravir on Clinical and Laboratory Findings of Patients with moderate COVID-19	Molnupiravir vs Placebo and Covid-19 routine care	Iran

History of using Molnupiravir in Covid-19 treatment

In April, 2020, the US food and drug administration (FDA) and the UK Medicines and Healthcare Products Regulatory Agency (MHRA) authorized the start of first phase of human trial for Molnupiravir which displayed that this drug combination is safe (1-2). Then the second phase of clinical trial has been approved. On March 6, 2021, the initial findings of randomized, double-blind, placebo-controlled clinical trial for phase 2 were announced by the manufacturer. In this study, 202 non-hospitalized adults have participated who had Covid-19 symptoms for seven days and their active infection was confirmed. The preliminary data of this study showed that among 202 participants under treatment, four serious side effects were reported none of which were related to drug intervention (2).

On December 23, the FDA issued the emergency use authorization of Molnupiravir for patients with mild-to-moderate Covid-19 who are at the high-risk of disease progression (including hospitalization or death). It must be prescribed within five days of symptom onset (8).

According to the announcement of FDA, this medication is not recommended for patients under 18 years of age because it affects their bone growth (8).

The quality of included clinical trial studies

The three studies are double-blind randomized controlled trials conducted by the manufacturing company. Based on published report, these studies seem to have an acceptable (relatively strong, relatively reliable and recommended).

Generally, there is conclusive evidence at a moderate level for the outcome of using this medicine in the following cases (7):

- The rate of hospitalization in patients with Covid-19
- The number of death caused by Covid-19
- Clinical progression of Covid-19
- Safety

Indications

Molnupiravir can be used to treat Covid-19 in hospitalized patients with mild, moderate or severe symptoms or in non-hospitalized patients with mild-to-moderate symptoms in the early stages of the disease (viral phase) (2).

Safety

Due to the mechanism of action of Molnupiravir, the potential of increasing new mutations emergence was closely investigated. Since, the mutations caused by this medicine were not clarified yet, it is not recommended during pregnancy and for who are planning to become pregnant (7).

In phase one of a clinical trial, the safety and tolerability of different dosage of Molnupiravir were evaluated in participants with Covid-19 symptoms. In this study, it was observed that 800 mg of Molnupiravir twice a day for 5 days is safe and well-tolerated in patients with severe symptoms of Covid-19 (5). 18 participants out of 103 investigating volunteers enrolled in the study between June 17, 2020 and October 30, 2020. Molnupiravir was well-tolerated at doses of 300, 600 and 800 mg without serious or severe side effects (5). In general, 4 out of 4 (100%), 4 out of 4 (100%) and 1 out of 4 (25%), participants in the 300, 600 and 800 mg Molnupiravir groups, respectively and 5 out of 6 patients in the control groups, experienced at least one side effect (all of which were mild) (5). (Table 4).

Table 4. Molnupiravir safety status.

	Molnupiravir 300 mg	Molnupiravir 600 mg	Molnupiravir 800 mg	Standard Care
Percentage of patients who experienced at least one side effect	100%	100%	25%	83.3%
Serious Observed Side effects	Number of patients			
Cardiac Disorders	0	0	1	0
Heartbeat	0	0	1	0
Digestive Disorders	2	3	0	2
Stomach Ache	1	0	0	0
Diarrhea	2	1	0	1
Indigestion	0	1	0	0
Nausea	1	2	0	1
Non-cardiac Chest Pain	0	0	0	1
Chest Pain	1	0	0	1
Respiratory, Chest and Mediastinum Disorders	1	1	0	1

Efficacy

In phase 2 of a double-blind multicenter placebo-controlled randomized trial, the antiviral effect of Molnupiravir (200 mg, 400 mg and 800 mg, twice daily for 5 days) was investigated in patients with mild-to-moderate symptoms of Covid-19. In general, Molnupiravir, especially the 800 mg dose, twice daily for 5 days, was effective in term of viral clearance (4).

In this clinical trial, 202 of 204 randomly selected participants received at least one dose of Molnupiravir or placebo, between June 19, 2020 and January 25, 2021, in 10 regions of the United States. Seven participants withdrew from the study due to side effects or not participating in follow-ups or based on physicians' decisions (4).

The Covid-19 test results of patients who received the Molnupiravir 800 mg, twice daily for 5 days, three days after drug administration (1.9% vs. 16.7%, P = 0.016) and five days after using medicine (0 vs. 11.1%, P = 0.03) were significantly less positive comparing to those who received the placebo (Table 5) (4).

The reduction of positive Covid-19 test, only 5 days after starting treatment, among patients who received 400 mg of Molnupiravir twice daily for 5 days, comparing to placebo was significant (0% vs. 1.11%, P = 0.03). Patients who received 200 mg of Molnupiravir were not significantly different from patients with positive Covid-19 test comparing to placebo (Table 5) (4).

The viral clearance time of Covid-19 was significantly decreased in participants receiving 800 mg of Molnupiravir (Median: 14 days, 95% confidence interval 13 to 14), comparing to placebo (Mean: 15 days; 95% confidence interval 15 to 27) (4).

The ratio of patients with negative Covid-19 test results in Molnupiravir 800 mg group was 92.5%, followed by 91.3% in Molnupiravir 200 mg group, 80.3% in placebo group and 78.7% in Molnupiravir 400 mg group (Table 5) (4).

In this study, no significant differences in side effects were observed between the groups (Molnupiravir 200 mg: 47.8%, Molnupiravir 400 mg: 32.3%, Molnupiravir 800 mg: 20%, placebo: 29%) (4).

Table 5. Results of phase two of clinical trials of Molnupiravir.

Intervention	Molnupiravir 200 mg	Molnupiravir 400 mg	Molnupiravir 800 mg	Placebo
Number of patients with positive Covid-19 test during the study				
One day after treatment	50%	41.9%	38.5%	47.2%
Three days after treatment	18.2%	11.6%	1.9%	16.7%
Five days after treatment	4.5%	0	0	11.1%
Number of patients with negative Covid-19 test during the study				
Time Median (with 95% confidence interval), days	22 (15-28)	27 (15-28)	14 (13-14)	15 (15-27)
Number of participants with negative Covid-19 test in the end of the study (%)	91.3%	78.7%	92.5%	80.3%

The third phase of clinical trial of this medicine was conducted on adults with mild-to-moderate Covid-19 who were at risk of severe disease progression. In this trial, 1433 participants were randomized, of which 716 patients received Molnupiravir and 717 received placebo. 6.8% (48 out of 707 patients) of whom they received Molnupiravir hospitalized vs 9.6% (68 out of 699 patients) of the placebo group. 0.1% died in the Molnupiravir group, while it was 1.3% for the placebo group. Early treatment with Molnupiravir reduces the risk of hospitalization or death in high-risk and unvaccinated adults with Covid-19 (6-7).

Probable prediction in miscellaneous reports

According to a news report published by Nature Publications on October 8, 2021, the following content has been released: "A pill can make it much easier and more effective to treat patients in the early stages of infection. It can also prevent hospitals from overflowing, especially in places where vaccination rates are still low, such as in many low- and middle-income countries." (9).

The cost of Molnupiravir

According to the manufacturing company, in the United States, each drug package is priced at $ 712 for a 5-day treatment period (10).

Discussion

Vaccines must play the frontline role in protection against Covid-19. The availability of medicines with different mechanisms of action provides an opportunity to develop combination therapies that potentially are synergistic and less likely to lead to resistance (11).

Molnupiravir is the first oral antiviral medicine which indicates significant benefits in reducing the rate of hospitalization or death in patients with mild Covid-19 and could be an important defense against Covid-19. However,

its role in treatment of moderate-to-severe Covid-19 is vague yet and further studies will be needed (8).
No adverse safety signals for this medication have been found and no dose-limiting toxicity was observed at the highest dose (800 mg). Also, there were no significant abnormalities in blood, pancreatic or hepatic parameters as a function of dose or treatment (11).
Molnupiravir may be prescribed orally, outside of healthcare centers, potentially as soon as Covid-19 is diagnosed. This medicine can be used to facilitate early treatment (12).
Three new oral antiviral drugs (Molnupiravir, Fluvoxamine, and Paxlovid) are effective in reducing mortality and hospitalization rates in patients with Covid-19. In addition, these three medicines demonstrated good immunity (12).

Conclusion

Based on the results of this review, it can be concluded that Molnupiravir can be used in outpatients and inpatients (over 18 years of age) with moderate and severe symptoms in the early stages of the disease but it is not recommended during pregnancy or for who are planning to become pregnant.

Acknowledgements

The present study is the result of the rapid response report about Molnupiravir which was commissioned by the Research Deputy of Ministry of Health and Medical Education as well as the National Institute of Health Research.

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