Molnupiravir: A new candidate for COVID-19 treatment

Fariba Pourkarim[1], Samira Pourtaghi-Anvarian[1], and Haleh Rezaee[2]

[1]Tabriz University of Medical Sciences
[2]Affiliation not available

April 05, 2024

Abstract

The novel coronavirus disease 2019 (COVID-19) emerged in late December 2019 in china and has rapidly spread to many countries around the world. The effective pharmacotherapy can reduce the mortality of COVID-19. Antiviral medications are the candidate therapies for the management of COVID-19. Molnupiravir is an antiviral drug with anti-RNA polymerase activity and currently is under investigation for the treatment of patients with COVID-19. This review focuses on summarizing published literature for the mechanism of action of molnupiravir in COVID-19, safety, efficacy, and clinical trials of molnupiravir in the treatment of COVID-19 patients.

Article type: Review article

Molnupiravir: A new candidate for COVID-19 treatment

Fariba Pourkarim[1,2], Samira Pourtaghi-Anvarian[2], Haleh Rezaee[2,3]

[1]Student Research Committee, Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran.

[2]Department of Clinical Pharmacy, Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran.

[3]Infectious Diseases and Tropical Medicine Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.

Running title: Molnupiravir in COVID-19

Corresponding Author: Dr. Haleh Rezaee,

Department of Clinical Pharmacy, Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran.

Fax: +984133344798.

Email: Rezaeeha@tbzmed.ac.ir; Rezaeehale91@gmail.com

Conflicts of Interest

The authors declare that there is no conflict of interest.

Abstract:

The novel coronavirus disease 2019 (COVID-19) emerged in late December 2019 in china and has rapidly spread to many countries around the world. The effective pharmacotherapy can reduce the mortality of COVID-19. Antiviral medications are the candidate therapies for the management of COVID-19. Molnupiravir is an antiviral drug with anti-RNA polymerase activity and currently is under investigation for the treatment of patients with COVID-19. This review focuses on summarizing published literature for the mechanism of action of molnupiravir in COVID-19, safety, efficacy, and clinical trials of molnupiravir in the treatment of COVID-19 patients.

Keywords: Molnupiravir; COVID-19 treatment; antiviral drugs; EIDD-2801; novel coronavirus disease 2019; MK-4482.

1 – Introduction

On December 2019, novel coronavirus disease 2019 (COVID-19) was recognized to cause a cluster of pneumonia cases in Wuhan, China [1, 2]. It has rapidly spread to other areas of the world [2-4]. On March 2020, the World Health Organization (WHO) declared COVID-19 as a global pandemic [5]. As of 28 May 2021, there have been 168 509 636 confirmed cases of COVID-19, including 3 505 534 deaths, reported to WHO [6]. COVID-19 is an enveloped, and positive single-stranded RNA virus and belongs to the *Coronaviridae* family of viruses [7]. Person-to-person contact and respiratory droplets are the two major routes of transmission of COVID-19 infection to humans. The usual incubation period for COVID-19 is 14 days [8]. Final diagnosis of COVID-19 is based on real-time reverse-transcriptase-polymerase chain reaction method [9, 10]. Clinical manifestations of COVID-19 are fever, dry cough, sore throat, shortness of breath, fatigue, headache, loss of taste or smell, diarrhea and nausea [2, 3, 11, 12]. Based on the epidemiologic data, COVID-19 has a lower mortality rate with higher degree of infectivity than the severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) [13, 14]. But, underling disease (i.e. hypertension, diabetes, and cancer) could increase mortality in COVID-19 patient [15]. Antiviral pharmacotherapy was considered for the treatment of COVID-19 because antiviral drugs used previously for the treatment of respiratory diseases associated with RNA viruses such as MERS, SARS, and Ebola virus (EBoV) [16, 17]. Molnupiravir (EIDD-2801, MK-4482), a ribonucleoside analog with a broad-spectrum antiviral activity, inhibits replication of virus by inhibition of RNA-dependent RNA polymerase (RdRp) activity [18]. It reduced replication of COVID-19 virus in hamster infection model and has been suggested as a candidate treatment for COVID-19 patients [18]. We aimed to review the clinical

evidence about the safety and efficacy of the use of molnupiravir in the treatment of patients with COVID-19.

2 - Mechanism of action of molnupiravir in COVID-19

Molnupiravir is an isopropyl ester prodrug of ′B-D-N4-hydroxycytidine (known, EIDD-1931 or NHC) [23]. EIDD-1931, a ribonucleoside analog, was developed primarily against the influenza virus. Recently, its antiviral effects against SARS-CoV and COVID-19, were reported in cell lines and culture media containing airway epithelial cells [19-21]. Based on the results of studies, EIDD-1931 inhibits the replication of many viruses, including influenza virus type A and B, EBoV, MERS-CoV, and encephalitis viruses [19, 22]. The chemical synthesis of molnupiravir from uridine consists of 5 steps characterized by multiple extractions and tiresome purification processes. Currently, chemoenzymatic processes used to EIDD-2801 synthesis with 75% efficiency [20, 24, 25]. EIDD-1931 appears to affect mitochondrial function of viruses but in-vitro studies show no significant toxicity effects on mitochondrial function [26]. Molnupiravir inhibits the RdRp enzyme of COVID-19, and causes several errors in the RNA virus replication [27]. In other words, molnupiravir can reduce the pathogenesis and replication of coronaviruses like remdesivir. The results of docking study showed that the limited space of mutations in the drug structure can cause the inhibitory effects of molnupiravir on the appearance of drug resistance-related mutations. Therefore, molnupiravir can be effective in treating patients with resistant to remdesivir [28].

3 - Clinical consideration and drug interactions of molnupiravir

Based on pharmacokinetic studies, molnupiravir should be administered twice daily to provide an adequate concentration in the respiratory tissues [23]. Based on the results of clinical trials,

molnupiravir is well absorbed orally and shows linear pharmacokinetics between doses of 50-1600 mg. Administration of molnupiravir with food may significantly decrease the rate of absorption. However, the extent of absorption is similar in both with or without food. Therefore, the administration of molnupiravir with food is conflicting [29]. Headache, nausea, and diarrhea are the most common adverse effects of molnupiravir. Other adverse effects include influenza-like syndrome, back pain, rhinorrhea, hot flashes, and pain in extremity [22, 29]. Trace amounts of molnupiravir found in the urine [29]. There are no comprehensive studies about its metabolism in the body, blood carriers, and drug-drug interactions [30]. Therefore, more studies are needed to clarify the metabolism and drug-drug interactions of molnupiravir. Due to the potential of molnupiravir for teratogenicity, it should not be used during pregnancy until further studies clarify their teratogenicity risk [23].

4 - Molnupiravir in COVID-19; published studies

Several studies have investigated the inhibitory effects of molnupiravir on COVID-19 replication in animal models. In the study conducted by Wahl et al., [26] the effects of EIDD-2801 on lung infection were investigated in mice. In this study, lung-only mice (LoM) was used as an in vitro model to assess lung infection. In order to creation of LoM model, human lung tissue was implanted subcutaneously in the back of male and female mice with 12-21 weeks old. Then, eight weeks after surgery, these animal models were used for the experimental process. EIDD-2801 was started 12-48 hours after infection and administered every 12 hours. A significant reduction in the number of viruses in lung tissue is apparent two days after the start of treatment. For evaluating the prophylactic effects, molnopiravir was started 12 hours before infection. The results showed that molnopiravir is more effective in the prevention of COVID-19 infection if it is started earlier. Cox et al. [31] investigated the effects of EIDD-2801 in inhibiting COVID-19 transmission in

ferrets. In this study, EIDD-2801 was used as BID, 12 and 36 hours after infection by oral gavage. Also, the effect of molnupiravir on blocking contact transmission were investigated (in the control and drug groups). Based on the results, it blocks the virus transmission 24 hours after administration. In another study conducted by Rosenke et al., [32] the inhibitory effects of EIDD-2801 on COVID-19 replication were evaluated in Syrian hamster lung epithelial cells and the results showed a significant reduction in virus replication. In a study conducted by Abdelnabi et al., [18] the administration of molnopiravir reduced the virus titer and the RNA load of the virus in a dose-dependent manner compared with the control group. The study has also demonstrated that delaying therapy may not stop the virus replication. But, the progression of the infection in the hamster's lungs maybe has a delay. In a similar study conducted by Abdelnabi et al. [21] the effect of combination therapy with favipiravir and molnupiravir on the COVID-19 infection was evaluated. In this study, molnupiravir administered at doses of 75, 150, 200, and 500 mg/kg BID for 4 days (starting treatment 1 hour before infection), and showed a dose-dependent decrease in virus RNA copies and virus load into lung tissue. If treatment is started 24 hours after infection, it may not effectively reduce the virus replication but, it can slow the progression of COVID-19. In this study, a reduction in virus and RNA loading was observed with high doses of favipiravir (300 and 500mg/kg). In addition, the combination therapy of molnupiravir and favipiravir increases the number of mutations in the RNA structure dramatically compared with favipiravir or molnupiravir alone, which in turn significantly reduces the RNA titer [21]. The details of these studies are given in Table 1.

5 - Molnupiravir in COVID-19; ongoing clinical trials

Based on clinicaltrials.gov database until 24 April 2021, five clinical trials are being conducted to evaluate the efficacy and safety of molnupiravir in COVID-19 patients (Table 2). Among them,

one study is based in the United Kingdom, and four study are multi-country. Study sample size ranges from 204 to 1450, with a cumulative sample size of 5004. Molnupiravir is administered orally at a doses of 50 mg to 800 mg in each clinical trials. The severity of COVID-19 ranges from mild to severe. One clinical trial evaluates the efficacy and safety of molnupiravir, nitazoxanide, and monoclonal antibody VIR-7832 in COVID-19 infection. Other trials compare the efficacy of molnupiravir with placebo or standard of care. The primary endpoints of studies are time-to-sustained recovery, determination of safety and tolerability of single and multiple ascending doses of molnupiravir, the occurrence of adverse event, the occurrence of any adverse events as assessed by Kaplan Meier approach, reduction in serious complications of COVID-19 such as hospitalization, reduction in SAO2<92% or death, virologic clearance rates after oral administration of EIDD-2801, hospitalization rate and/or death, the occurrence of serious adverse events as assessed by division of acquired immunodeficiency syndrome (DAIDS). In a Phase 1 clinical trial [29], healthy subjects with age between 18 and 60 years, and body mass index between 18 and 30 kg/m^2 were randomized in a 3:1 ratio to receive single dose of molnupiravir, multiple dose of molnupiravir, or placebo for 5.5 days. Subjects were followed for 14 days to assess the safety, tolerability, and pharmacokinetics of molnupiravir. Maximum serum concentrations reached in 1 to 1.75 hours after oral administration of molnupiravir. Its biologic half-life is approximately 1 hours. Common adverse effects are headache and diarrhea, which was lower in the molnupiravir group (12.5%) compared to the placebo group (18.8%) and 93.3% of adverse effects were mild. The results of this study showed that molnupiravir is well-tolerated. One subject was discontinued early due to skin rash. To evaluate the effect of food on pharmacokinetics of molnupiravir, subjects were randomized in a 1:1 ratio to receive 200 mg molnupiravir in the fed state or 200 mg molnupiravir under fasting conditions. There was a reduction in the absorption rate, but no decrease in overall exposure.

6 - Conclusion

The RdRp is an essential enzyme for COVID-19 replication and seems to play a key role in the pathophysiology of COVID-19. Molnupiravir targets RdRp and is a candidate drug for COVID-19 treatment. Based on animal studies, molnupiravir can be effective in COVID-19, but well-designed randomized clinical trial studies are required in the future to confirm the therapeutic effects of molnupiravir in patients with COVID-19.

DISCLOSURES

The authors declare that there is no conflict of interest.

References

1. Lu H, Stratton CW, Tang YW. Outbreak of pneumonia of unknown etiology in Wuhan, China: the mystery and the miracle. J Med Virol 2020; 92: 401-2.
2. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395: 497-506.
3. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020; 395: 507-513.
4. Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. Lancet 2020; 395: 470-473.
5. Baradaran H, Hamishehkar H, Rezaee H. NSAIDs and COVID-19: a new challenging area. Pharm Sci 2020; 26: S49-51.
6. World Health Organization: Coronavirus disease (COVID-19) Situation dashboard. World Health Organization; Updated 2021/05/28, 2:00 pm CEST. https://covid19.who.int.
7. Ciotti M, Angeletti S, Minieri M, Giovannetti M, Benvenuto D, Pascarella S, Sagnelli C, Bianchi M, Bernardini S, Ciccozzi M. COVID-19 outbreak: an overview. Chemotherapy 2019; 64: 215-23.
8. Rezaee H, Pourkarim F, Pourtaghi-Anvarian S, Entezari-Maleki T, Asvadi-Kermani T, Nouri-Vaskeh M. Drug-drug interactions with candidate medications used for COVID-19 treatment: An overview. Pharmacol Res Perspect 2021; 9: e00705.
9. Corman VM, Landt O, Kaiser M, Molenkamp R, Meijer A, Chu DK, Bleicker T, Brünink S, Schneider J, Schmidt ML, Mulders DG. Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. Euro Surveill 2020; 25: 2000045.
10. Rubin EJ, Baden LR, Morrissey S, Campion EW. Medical journals and the 2019-nCoV outbreak. N Engl J Med 2020; 382: 866.
11. National Center for Health Statistics, & Centers for Disease Control and Prevention. 2020. COVID-19 Data from the National Center for Health Statistics.

https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html. Accessed April 1, 2020.
12. Lechien JR, Chiesa-Estomba CM, Hans S, Barillari MR, Jouffe L, Saussez S. Loss of smell and taste in 2013 European patients with mild to moderate COVID-19. Ann Intern Med 2020; 173: 672-5.
13. World Health Organization. Coronavirus disease (COVID-19) weekly epidemiological update. 2020. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200824-weekly-epi-update.pdf?sfvrsn=806986d1_4. Accessed August 24, 2020.
14. Gorbalenya AE, Baker SC, Baric RS, de Groot RJ, Drosten C, Gulyaeva AA, Haagmans BL, Lauber C, Leontovich AM, Neuman BW, Penzar D. Coronaviridae Study Group of the International Committee on Taxonomy of Viruses. The species severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. Nat Microbiol 2020; 5: 536-44.
15. Nouri-Vaskeh M, Kalami N, Zand R, Soroureddin Z, Varshochi M, Ansarin K, Rezaee H, Taghizadieh A, Sadeghi A, Ahangari Maleki M, Esmailnajad A. Comparison of losartan and amlodipine effects on the outcomes of patient with COVID-19 and primary hypertension: A randomised clinical trial. Int J Clin Pract 2021; e14124.
16. Venkatasubbaiah M, Reddy PD, Satyanarayana SV. Literature-based review of the drugs used for the treatment of COVID-19. Curr Med Res Pract 2020; 10: 100-9.
17. YAVUZ S, Ünal S. Antiviral treatment of COVID-19. Turk J Med Sci 2020; 50: 611-9.
18. Abdelnabi R, Foo CS, Kaptein SJ, Zhang X, Langendries L, Vangeel L, Vergote V, Heylen E, Dallmeier K, Chatterjee A, De Jonghe S. Molnupiravir (EIDD-2801) inhibits SARS-CoV2 replication in Syrian hamsters model. bioRxiv 2020.
19. Vicenti I, Zazzi M, Saladini F. SARS-CoV-2 RNA-dependent RNA polymerase as a therapeutic target for COVID-19. Expert Opin Ther Pat 2021; 1-13.
20. Paymode DJ, Vasudevan N, Ahmad S, Kadam AL, Cardoso FS, Burns J, et al. Toward a Practical, Two-Step Process for Molnupiravir from Cytidine. 2021.
21. Abdelnabi R, Foo CS, Kaptein SJ, Zhang X, Langendries L, Vangeel L, et al. The combined treatment of Molnupiravir and Favipiravir results in a marked potentiation of efficacy in a SARS-CoV2 hamster infection model through an increased frequency of mutations in the viral genome. bioRxiv 2021; 2020-12.
22. Painter WP, Holman W, Bush JA, Almazedi F, Malik H, Eraut NC, et al. Human Safety, Tolerability, and Pharmacokinetics of a Novel Broad-Spectrum Oral Antiviral Compound, Molnupiravir, with Activity Against SARS-CoV-2. medRxiv 2020.
23. Toots M, Yoon J-J, Hart M, Natchus MG, Painter GR, Plemper RK. Quantitative efficacy paradigms of the influenza clinical drug candidate EIDD-2801 in the ferret model. Transl Res 2020; 218: 16-28.
24. Del Arco J, Acosta J, Fernández-Lucas J. New trends in the biocatalytic production of nucleosidic active pharmaceutical ingredients using 2′-deoxyribosyltransferases. Biotechnol Adv 2021; 107701.
25. Vasudevan N, Ahlqvist GP, McGeough CP, Paymode DJ, Cardoso FS, Lucas T, et al. A concise route to MK-4482 (EIDD-2801) from cytidine. Chem comm 2020; 56: 13363-4.
26. Wahl A, Gralinski LE, Johnson CE, Yao W, Kovarova M, Dinnon KH, et al. SARS-CoV-2 infection is effectively treated and prevented by EIDD-2801. Nature 2021; 591: 451-7.

27. Thakur S, Sarkar B, Ansari AJ, Khandelwal A, Arya A, Poduri R, et al. Exploring the magic bullets to identify Achilles' heel in SARS-CoV-2: Delving deeper into the sea of possible therapeutic options in Covid-19 disease: An update. Food Chem Toxicol 2021; 147: 111887.
28. Padhi AK, Shukla R, Saudagar P, Tripathi T. High-throughput rational design of the remdesivir binding site in the RdRp of SARS-CoV-2: implications for potential resistance. Iscience 2021; 24: 101992.
29. Painter WP, Holman W, Bush JA, Almazedi F, Malik H, Eraut NC, et al. Human Safety, Tolerability, and Pharmacokinetics of Molnupiravir, a Novel Broad-Spectrum Oral Antiviral Agent with Activity Against SARS-CoV-2. Antimicrob. Agents Chemother 2021; 65.
30. Kumar D, Trivedi N. Disease-drug and drug-drug interaction in COVID-19: risk and assessment. Biomed Pharmacother 2021; 111642.
31. Cox RM, Wolf JD, Plemper RK. Therapeutically administered ribonucleoside analogue MK-4482/EIDD-2801 blocks SARS-CoV-2 transmission in ferrets. Nat Microbiol 2021; 6: 11-8.
32. Rosenke K, Hansen F, Schwarz B, Feldmann F, Haddock E, Rosenke R, et al. Orally delivered MK-4482 inhibits SARS-CoV-2 replication in the Syrian hamster model. Nat Commun 2021; 12: 1-8.

Table 1. Clinical studies published for the therapeutic effects of Molnupiravir in COVID-19

Study, Year	Infection Model	Route of Infection by SARS-CoV-2	Dose of Molnupiravir	Other Treatments	Follow-Up Time	Outcomes
Wahl et al. , 2021	Mice	Direct injection into lung tissue on LoM	-	-	Days 2, 6, and 14 after infection	Reducing the replication and amount of infectious particles in lung tissue
Cox et al. , 2021	Ferrets	Intranasal	5 or 15 mg/kg BID 12 hours post infection And 5mg/kg BID 36 hours post infection For blocking contact transmission: Control group: vehicle (methyl cellulose 1%) Drug group: EIDD-2801, 5 mg/kg BID	-	24 hours after initiation of treatment	undetectable viral particles in the respiratory system and blocking contact transmission of the virus
Rosenke et al. , 2021	Syrian hamster	Intranasal	250 mg/kg BID (12 hours pre-infection and 12 hours post-infection groups) Vehicle (control group)	-	Fourth day after infection	Reduction in the replication of SARS-CoV-2 viruses
Abdelnabi et al. 2020	Syrian Gold hamster	Intranasal	75 or 200 mg/kg BID(Start administration 24-48 hours after infection) for 4 days	-	-	Dose-dependent reduction in viral RNA load and virus titer
Abdelnabi et al. 2021	Syrian Gold hamster	Intranasal	150 mg/kg BID	Favipiravir (300mg/kg BID Intra-peritoneal injection)	-	Reduction in viral RNA load and virus titer Increasing the number of mutations in the RNA structure

Table 2. Summary of ongoing clinical trials investigating the therapeutic effects of molnupiravir for the treatment of COVID-19

ID	Status	Design	Country	Population (n = patients)	Intervention group(s)	Comparison group(s)	Primary outcomes
NCT04575584	Recruiting	Randomized, double-blind, placebo-controlled trial	Multicounty	N= (1300)	200 mg or 400 mg or 800 mg molnupiravir orally every 12 hours for 5 days	Placebo administered orally every 12 hours for 5 days	Time-to-sustained recovery Percentage of participants with an adverse event Percentage of participants who discontinued study intervention due to an adverse event
NTC04746183	Recruiting	Open-label, randomized clinical trial	United Kingdom	N=(600)	molnupiravir administered orally, twice daily for 10 doses or nitazoxanide administered orally, initially twice daily for 14 doses with starting dose 1500 mg BID or VIR-7832 administered IV infusion with starting dose 50 mg	Placebo or standard of care (in phase 1b)	Master protocol: Dose-finding /Phase I Master protocol: efficacy evaluation/Phase II - severe patients Master protocol: efficacy evaluation/Phase II – mild to moderate patients CST-2 Phase I: to determine the safety and tolerability of multiple ascending doses of molnupiravir to recommend dose for phase II. CST-2 Phase II: to determine the ability of molnupiravir to reduce serious complications of COVID-19 including hospitalization, reduction in SAO2<92%, or death.
NCT04405570	Completed	Randomized, double-blind, placebo-controlled trial	Multicounty	N= (204)	EIDD-2801 twice daily (BID) for 5 days	Placebo oral capsule	Virologic efficacy Number of participants with any adverse events as assessed by Kaplan Meier approach
NCT04575597	Recruiting	Randomized, placebo-controlled, double-blind clinical trial	Multicounty	N= (1450)	molnupiravir administered orally in capsule form every 12 hours for 5 days	Placebo matching molnupiravir administered orally in capsule form every 12 hours for 5 days	Percentage of participants who are hospitalized and/or die Percentage of participants with an adverse event Percentage of participants who discontinued study intervention due to an adverse event
NCT04405739	Recruiting	Randomized, placebo-controlled, double-blind clinical trial	Multicounty	N= (1450)	EIDD-2801 administered orally twice daily for 5 days	Placebo oral capsule twice daily for 5 days	Number of participants that achieve virologic clearance after oral administration of EIDD-2801 Number of participants with any serious adverse events as assessed by DAIDS

IV; intravenous, CST; candidate-specific trial, DAIDS; division of acquired immunodeficiency syndrome.