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Molnupiravir in Combination with Remdesivir for Severe COVID-19 Patients Admitted to Hospital: a Case Series

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Abstract

Since the start of the COVID-19 pandemic, a large number of trials have examined the efficacy of various medications as potential treatments for COVID-19, but a promising therapeutic option is still missing and under investigation. Molnupiravir is an investigational oral antiviral medication and a nucleoside analogue that suppresses SARS-CoV-2 replication and has been found to be active against common virus variations (including the Delta variant). Several phase 2 and 3 clinical trials have shown high efficacy for direct antiviral activity of molnupiravir as well as its favorable safety and tolerability in mild to moderate Covid-19 patients. The current study was done on five hospitalized, severe COVID-19 patients. It seems that in combination with remdesivir, this novel antiviral could exert a synergistic effect on reducing the severity of symptoms as well as the duration of hospitalization. However, further clinical studies on the use of molnupiravir in the treatment of severe COVID-19 are warranted.

Key word: SARS-CoV-2, COVID-19, molnupiravir, remdesivir, severe patients, hospitalized.

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Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has expanded globally since its emergence in Wuhan, China in December 2019, resulting in a global pandemic with more than 458 million confirmed cases and about 6 million deaths documented as of March 15, 2022 (1, 2). SARS-CoV-2 variants are spreading in diverse parts of the world, raising a new concern of greater virus dissemination and the ability to evade both vaccine and infection-induced immunity (3). Despite numerous trials examining the efficacy of various prospective drugs, promising therapeutic alternatives for treating Coronavirus Disease 2019 (COVID-19) are still missing (4).

Due to the contagious nature of the disease, the current focus is mainly on the development of new antiviral drugs and vaccines. One of the medications being developed in this field is molnupiravir. Molnupiravir is an investigational oral antiviral medication and a nucleoside analogue that suppresses SARS-CoV-2 replication which is active against common virus variations (including the Delta variant) (5). It is not yet clinically accessible. U.S. Food and Drug Administration advisory committee has narrowly endorsed molnupiravir, a COVID-19 pill developed by Merck, for the treatment of mild to moderate COVID-19 in patients at risk of developing a severe form of the disease (MOVe-OUT trial (MK-4482-002) (NCT04575597)). In Syrian hamsters and ferrets, molnupiravir, the orally accessible prodrug of the nucleoside analogue N4-hydroxycytidine, was efficacious against SARS-CoV-2 infections (6, 7). Reports from a phase 2a trial (NCT04405570) indicated high efficacy for direct antiviral activity as well as favorable safety and tolerability of molnupiravir in Covid-19 outpatients (8).

As molnupiravir was used in mild to moderate COVID-19 patients, the efficacy and safety of the medicine have not yet been evaluated in severe cases. In this case-series study, molnupiravir was administered to hospitalized patients with severe SARS-CoV2 infection.

Materials and Methods

Setting

Between September and November 2021, the current study was conducted on adult COVID-19 patients at Masih Daneshvari Hospital, a university-affiliated and authorized referral hospital for COVID-19, Tehran, Iran.

Patients

Subjects under the age of 18 who had COVID-19 confirmed by reverse transcriptase-polymerase chain reaction (RT-PCR) and met the following criteria were enrolled in the study: Acute respiratory distress syndrome (PaO2/FiO2 less than 300 mmHg); oxygen saturation of equal or less than 94%; deteriorating state after 72 hours despite national COVID-19 guideline-recommended treatments; bilateral pulmonary infiltration. Patients with decompensated liver disease (Child-Pugh class C), stage 4 and 5 chronic kidney disease, and pregnant and lactating women were excluded from the study.

The study was approved by the Research Ethics Committee of Qom University of Medical Sciences (ethics code number: IR.MUQ.REC.1400.152).

Intervention

Severe COVID-19 patients who were admitted to the hospital and met our study inclusion criteria, in addition to supportive care (oxygen therapy and anticoagulation), received 800 mg molnupiravir twice daily for five days, along with remdesivir: (200 mg stat on day 1, followed by 100 mg intravenously, daily for 5 days) and dexamethasone (8 mg intravenously, daily up to the point of discharge or up to 10 days), according to the national guidelines for COVID-19.

Case 1

A 69-year-old woman was admitted to the hospital with severe COVID-19 pneumonia. She had been suffering from fever, chills, dyspnea, and vertigo for two days prior to admission.

Her medical history included hypertension, diabetes, and minor thalassemia. Interleukin-6 and procalcitonin (PCT) levels were normal, but elevated C-reactive protein (CRP) was detected (135 mg/L) and RT-PCR was positive. In the inferior zone, a computed tomography (CT) scan revealed symmetric bilateral ground-glass opacities. She was given non-invasive ventilation (NIV).

The patient's general condition improved after five days of molnupiravir treatment, and her fever, tachypnea, and retraction gradually decreased. The oxygen saturation in the air room increased from 87 to 92 percent, whereas CRP dropped to 13 mg/L. Improvement in radiological abnormalities on CT scan was noted after seven days, and RT-PCR turned negative.

Case 2

A 34-year-old woman was hospitalized with COVID-19 pneumonia. She had fever, cough, and myalgia since the day before admission.

She did not appear to have any underlying disease or immunological deficit. Interleukin-6 and procalcitonin levels were 2 pcg/mL and 0.02 ng/ml, respectively. A modest CRP elevation (15 mg/L) was seen, and RT-PCR was positive. The initial chest CT scan revealed ground-glass opacities in the inferior zone on both lungs. She received a molnupiravir/remdesivir regimen as well as oxygen support (3 liters per minute). The patient's general condition improved after 48 hours and the fever and cough disappeared.

After seven days, her radiological abnormalities on CT scan had improved, RT-PCR was negative, and CRP dropped to 2 mg/L.

Case 3

A 60-year-old woman with severe COVID-19 pneumonia was admitted to the hospital. For three days prior to admission, she had been suffering from fever, dyspnea, and myalgia.

Hypertension, dyslipidemia, and hypothyroidism were among her medical conditions. CRP (33 mg/L), IL-6 (90 pcg/mL), and procalcitonin (0.05 ng/ml) levels were elevated, and RT-PCR was positive. She had significant lymphopenia. The patient's CT scan demonstrated the ground-glass opacities and consolidation on both lungs.

Treatment included non-invasive ventilation (NIV). The patient's general status improved after five days of molnupiravir therapy. She was also given oxygen support (5 liters/min) as part of her treatment regimen. Fever and tachypnea went away after 5 days of treatment. Oxygen saturation in the air room increased from 80% to 90%, while CRP and IL-6 decreased to 2 and 19, respectively.

On the tenth day of his admission, the patient was discharged with a good overall condition and 90% oxygen saturation.

Case 4

A 30-year-old woman with COVID-19 pneumonia was hospitalized at Masih Daneshvari hospital emergency department. The patient's symptoms, including dyspnea and myalgia, had been rapidly deteriorating over six days before admission.

She had no underlying medical condition. PCT levels were normal, but CRP (16 mg/L) and IL-6 (71 pcg/mL) were increased, and RT-PCR was positive. She had lymphopenia on admission.

The ground-glass opacity was seen in large areas in both lungs during the CT scan. A nasal oxygen mask (10

Liter/min) was administered to the patient.

After seven days of molnupiravir therapy in addition to a decrease in the need for oxygen support (3 liters/min) (on day 13 of symptoms onset), the patient's general condition was improved. The fever and tachypnea were no longer present.

The patient's oxygen saturation in the air room improved from 88 to 92 percent, while CRP and IL-6 dropped to 1 and 18, respectively. The patient was discharged 14 days after her hospitalization with 95 percent oxygen saturation and a good overall condition.

Case 5

A 56-year-old man with COVID-19 pneumonia was hospitalized in the emergency department. He had dyspnea, a non-productive cough, fatigue, and myalgia for five days prior to admission. Three days before admission, he was given Favipiravir tablet 600 mg twice a day.

On the fourth day after symptoms onset, a CT scan indicated bilateral ground-glass opacities and consolidation. The patient had a past medical history of diabetes. PCT was within normal limits, but CRP (59 mg/L) and IL-6 (18 pcg/mL) were elevated, and RT-PCR was positive. He also suffered from Leukocytosis.

In order to treat his severe hypoxemia, he was given non-invasive ventilation (NIV). His general condition improved after seven days of molnupiravir therapy and he had no fever and tachypnea. He also was given oxygen support (3 liters/min) via Venturi oxygen mask. On this day, oxygen saturation in the air room increased from 75 to 90 percent, and CRP declined to 5 mg/L. With a 90 percent oxygen saturation, negative RT-PCR, and good overall condition, the patient was discharged seven days following his admission (table 1).

Discussion

In the present study, the effect of molnupiravir in addition to remdesivir, in five severe COVID-19 patients who were admitted to the hospital, was evaluated. RNA-dependent RNA polymerase (RdRp) is an enzyme that plays an essential role in the RNA virus replication process. Different levels of antiviral activity are seen in RdRp inhibitors as a result of the enzyme's conserved protein structure. Remdesivir, an RdRp inhibitor, was the first FDA (the US Food and Drug Administration)-approved drug for the management of COVID-19 in hospitalized patients that was firstly approved for severe cases and several months later, received approval for non-severe cases as well (9). However, recently, several remdesivir-resistant mutations of SARS-COV-2 have been identified in vitro and one case report showed resistance to remdesivir in an immunocompromised patient (10, 11). As concerns are rising over the emergence of antiviral-resistant SARS-COV-2, the need for developing new antiviral drugs and using effective antiviral regimens is still warranted.

Molnupiravir is another antiviral that received emergency use authorization from FDA for COVID-19 treatment in certain adults (12). According to phase-III MOVe-OUT trial (NCT04575597), molnupiravir decreased the risk of hospitalization or mortality by about half (7.3 versus 14.1 percent with placebo) in over 750 non-hospitalized patients with mild to moderate COVID-19 and at least one risk factor for severe illness. Both groups had an equal incidence of drug-related adverse events.

Two Phase-III double-blind, randomized, controlled, multicenter trial investigated the efficacy and safety of molnupiravir compared to placebo. One trial (NCT04575597) enrolled 1850 non-hospitalized patients, while the other had 304 hospitalized individuals (NCT04575584).

Since the use of molnupiravir has been assessed in mild to moderate COVID-19 patients in most trials conducted, ongoing studies, and its MHRA (Medicines and Healthcare products Regulatory Agency) approval, further investigation on severe and hospitalized cases is warranted. On the other hand, molnupiravir is a mutagenizing drug that interferes with viral replication by causing an 'error catastrophe' during this process (13). If the treatment is not completed, this mutation can contribute to the emergence of resistant species. As a result, to obtain an optimum therapeutic effect and to reduce the risk of resistance, a number of studies are evaluating combined antiviral therapy in patients with Covid-19. In one study, combination treatment with molnupiravir and favipiravir has shown a significant increase in antiviral efficacy in a SARS-CoV-2 hamster infection model (14). In another study, a combination of a Pyrimidine inhibitor (Brequinar) and a nucleoside analogue (Molnupiravir) was used both in vitro and in mice. A notable antiviral synergy was found with this regimen (15). Considering the aforementioned issues, the present study used a combination of molnupiravir with remdesivir in five hospitalized, severe COVID-19 patients. It seems that in combination with remdesivir, this novel antiviral could exert a synergistic effect on reducing the severity of symptoms as well as the duration of hospitalization. However, there is no specific result available in this regard. Moreover, as for many case series, there were several limitations in our study. The main limitations of the current study were as follows: small sample size and lack of a control group which limited accurate and thorough evaluation of the results. Finally, molnupiravir was added to remdesivir, based on national COVID-19 guidelines and a number of ethical issues. This addition may interfere with the evaluation of the net therapeutic effect of molnupiravir.

Conclusion

Molnupiravir is an oral, direct-acting antiviral against SARS-CoV-2. In COVID-19 patients undergoing five-day treatment, molnupiravir was substantially efficient in reducing patients' symptoms and had an acceptable safety and tolerability profile. Its application in individuals with SARS-CoV-2 infection requires more research to determine the exact impact of molnupiravir on the clinical course of COVID-19 and to assess if there is a subset of patients who will benefit the most from this therapy.

Table 1

Demographic, admission data and lab results of the five COVID-19 patients

	P1	P2	P3	P4	P5
Demographic data					
Age (year)	69	34	60	30	56
Sex	Female	Female	Female	Female	Male
Symptom Onset (days before admission)	2	1	3	6	5
Underlying diseases	hypertension, diabetes, minor thalassemia	None	Hypertension, dyslipidemia, hypothyroidism	None	diabetes
Admission Data					
O2 Saturation (without respiratory support) (%)	Day 1: 87 Day 7: 92	Day 1: 92 Day 7: 96	Day 1: 80 Day 7: 90	Day 1: 88 Day 7: 92	Day 1: 75 Day 7: 90
Respiratory Rate (breaths per minute)	28	18	22	20	25
Heart Rate (bpm)	60	80	100	50	50
BP (mmHg)	130/80	120/70	150/90	120/70	130/70
Lab results					
WBC (cells per microliter)	Day 1: 2400 Day 7: 6200	Day 1: 5400 Day 7: 5800	Day 1: 4400 Day 7: 8300	Day 1: 19700 Day 7: 10800	Day 1: 12900 Day 7: 11200
Lymph (%)	Day 1: 22 Day 7: 9.7	Day 1: 28 Day 7: 30	Day 1: 19 Day 7: 19	Day 1: 4 Day 7: 11	Day 1: 8 Day 7: 11
Neut (%)	Day 1: 71 Day 7: 80	Day 1: 54 Day 7: 55	Day 1: 77 Day 7: 72	Day 1: 91 Day 7: 83	Day 1: 90 Day 7: 85
IL-6 (pcg/mL)	Day 1: 5.9 Day 7: 4	Day 1: 2 Day 7: 2	Day 1: 90 Day 7: 19	Day 1: 71 Day 7: 18	Day 1: 18 Day 7: 5
PCT (ng/mL)	0.02	0.02	0.05	0.02	0.02
PCR	Day 1: Positive Day 7: Negative	Day 1: Positive Day 7: Negative	Day 1: Positive Day7: Negative	Day 1: Positive Day 7: Negative	Day 1: Positive Day 7: Negative
CRP (mg/L)	Day 1: 132 Day 7: 15	Day 1: 15 Day 7: 2	Day 1: 33 Day 7: 2	Day 1: 16 Day 7: 1	Day 1: 59 Day 7: 5
Mortality	No	No	No	No	No
ADR	No	No	No	No	No
ICU Admission	No	No	No	No	No

BP: Blood Pressure; WBC: White blood cells; Lymph: Lymphocyte; Neut: Neutrophil; IL-6: Interleukin-6; PCT: Procalcitonin; PCR: Polymerase Chain Reaction; CRP: C-reactive protein; ADR: Adverse Drug Reaction; ICU: Intensive Care Unit.

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References

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A Novel Coronavirus from Patients with Pneumonia in China. N Engl J Med. 2020; 382(8): 727-733.
2. WHO Coronavirus (COVID-19) Dashboard. Covid19.who.int. 2022 [cited 16 March 2022]. Available from: https://covid19.who.int/
3. Mohammadi M, Shayestehpour M, Mirzaei H. The impact of spike mutated variants of SARS-CoV2 [Alpha, Beta, Gamma, Delta, and Lambda] on the efficacy of subunit recombinant vaccines. The Brazilian Journal of Infectious Diseases. 2021;25(4): 101606.
4. Tabarsi P, Barati S, Jamaati H, Haseli S, Marjani M, Moniri A, et al. Evaluating the effects of Intravenous Immunoglobulin (IVIg) on the management of severe COVID-19 cases: A randomized controlled trial. International Immunopharmacology. 2021; 90: 107205.
5. Zhou S, Hill C, Sarkar S, Tse L, Woodburn B, Schinazi R, et al. β-d-N4-hydroxycytidine Inhibits SARS-CoV-2 Through Lethal Mutagenesis But Is Also Mutagenic To Mammalian Cells. J Infect Dis. 2021; 224(3): 415-419.
6. Abdelnabi R, Foo C, De Jonghe S, Maes P, Weynand B, Neyts J. Molnupiravir Inhibits Replication of the Emerging SARS-CoV-2 Variants of Concern in a Hamster Infection Model. J Infect Dis. 2021; 224(5): 749-753.
7. Cox R, Wolf J, Plemper R. Therapeutically administered ribonucleoside analogue MK-4482/EIDD-2801 blocks SARS-CoV-2 transmission in ferrets. Nat Microbiol. 2020; 6(1): 11-18.
8. Fischer W, Eron J, Holman W, Cohen M, Fang L, Szewczyk L, et al. Molnupiravir, an Oral Antiviral Treatment for COVID-

19. 2021. DOI: 10.1101/2021.06.17.21258639.
9. Hashemian S, Pourhanifeh M, Hamblin M, Shahrzad M, Mirzaei H. RdRp inhibitors and COVID-19: Is molnupiravir a good option?. Biomed Pharmacother. 2022; 146: 112517.
10. Szemiel A, Merits A, Orton R, MacLean O, Pinto R, Wickenhagen A et al. In vitro selection of Remdesivir resistance suggests evolutionary predictability of SARS-CoV-2. PLOS Pathogens. 2021; 17(9): e1009929.
11. Gandhi S, Klein J, Robertson A, Peña-Hernández M, Lin M, Roychoudhury P et al. De novo emergence of a remdesivir resistance mutation during treatment of persistent SARS-CoV-2 infection in an immunocompromised patient: a case report. Nature Communications. 2022; 13(1).
12. Coronavirus (COVID-19) Update: FDA Authorizes Additional Oral Antiviral for Treatment of COVID-19 in Certain Adults. U.S. Food and Drug Administration. 2022 [cited 5 April 2022]. Available from: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-additional-oral-antiviral-treatment-covid-19-certain
13. Kabinger F, Stiller C, Schmitzová J, Dienemann C, Kokic G, S. Hillen H, et al. Mechanism of molnupiravir-induced SARS-CoV-2 mutagenesis. Nature Structural & Molecular Biology. 2021; 28(9): 740-746.
14. Abdelnabi R, Foo C, Kaptein S, Zhang X, Do T, Langendries L, et al. The combined treatment of Molnupiravir and Favipiravir results in a potentiation of antiviral efficacy in a SARS-CoV-2 hamster infection model. eBioMedicine. 2021; 72: 103595.
15. Schultz D, Johnson R, Ayyanathan K, Miller J, Whig K, Kamalia B, et al. Pyrimidine inhibitors synergize with nucleoside analogues to block SARS-CoV-2. Nature. 2022. DOI: 10.1038/s41586-022-04482-x.