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Comparison of the acceptability and safety of molnupiravir in COVID-19 patients aged over and under 80 years

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ABSTRACT

Background: Molnupiravir is being widely used as a treatment for coronavirus disease 2019 (COVID-19); however, its acceptability and safety in older patients aged ≥ 80 years in real-world clinical practice is not well understood.

Methods: We conducted a single-centre retrospective study and assessed the outcome of patients with COVID-19 treated with molnupiravir according to the following criteria: (A) discontinuation rate of molnupiravir; (B) type, frequency, and severity of adverse events; (C) all-cause mortality within 30 days of the diagnosis of COVID-19.

Results: Forty-seven patients (46.1%) were aged ≥ 80 years (older patients) and 55 (53.9%) were aged < 80 years (younger patients). There were no significant differences in coexisting diseases and history of vaccination for COVID-19 between older and younger patients. Older patients were significantly more likely to have moderate disease (moderate 1 and 2) according to the Japanese Ministry of Health, Labour and Welfare classification than younger patients. During treatment, 8.5% of older patients and 1.8% of younger patients stopped taking molnupiravir, but the difference was not significant. Adverse events were observed in 39/102 (38.2%) patients. The most common adverse events were diarrhoea (9.8%), exacerbation of coexisting diseases (6.9%), bone marrow suppression (6.9%), liver dysfunction (5.9%), and loss of appetite (4.9%). Most adverse events were minor, ranging from grades 1 to 3. The all-cause mortality rate was 10.8%, and no molnupiravir-related deaths were observed.

Conclusions: Molnupiravir treatment is acceptable and safe in older patients with COVID-19 aged ≥ 80 years.

1. Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), had spread globally from Wuhan, China, at the end of 2019 and led to enormous medical, social, and economic impacts worldwide. As of September 2022, over 612 million people have been diagnosed with COVID-19 worldwide, and approximately 6.5 million patients have died [1]. With the development of several vaccines and multiple treatments, the pandemic is nearing its end. As of November 2022, remdesivir, molnupiravir, and ritonavir-boosted nirmatrelvir have been approved and used worldwide as antiviral drugs against COVID-19 [2,3]. Molnupiravir, having activity against SARS-CoV-2, is a small-molecule ribonucleoside prodrug of N-hydroxycytidine that exerts its antiviral action by introducing copying errors during viral RNA replication [4,5]. Molnupiravir was evaluated in a phase 3 MOVe-OUT study in adult patients with non-hospitalised, symptomatic, mild-to-moderate COVID-19 who had at least one risk factor for severe disease, and its effectiveness was proven [6]. Several

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clinical studies have shown that molnupiravir significantly reduces the risk of hospitalisation or death in high-risk patients with mild-to-moderate COVID-19 [7]. According to the latest Japanese COVID-19 treatment guidelines, patients who (a) had mild-to-moderate COVID-19, (b) were at risk of progressing to severe disease, and (c) were in the early stage from disease onset (within 5 days) were recommended to receive molnupiravir [8]. Japan is a hyper-aged society, and many patients with COVID-19 who are admitted to the hospital are older. Age is a risk factor for severe disease in older individuals, and antiviral treatment is recommended in this population. However, in clinical practice, there is little experience with the use of antiviral drugs in older individuals, and studies on their acceptability and safety are insufficient.

In this retrospective study, we compared the acceptability and safety of molnupiravir in COVID-19 patients aged over and under 80 years.

2. Methods

2.1. Patients and methods

This was a retrospective study conducted in the National Hospital Organization Kyoto Medical Centre (NHOKMC: Kyoto City, Japan). NHOKMC is located in the southern part of Kyoto City and serves as the core hospital for the region. It is a tertiary level medical institution that handles all levels of emergencies. At the request of the government, it established a ward dedicated to the management of patients with moderate to severe COVID-19. We retrospectively reviewed patients who received molnupiravir for the treatment of COVID-19. All patients who received molnupiravir at NHOKMC were included in the study, and there are no exclusion criteria. All patients were diagnosed with COVID-19 using polymerase chain reaction (PCR)-based methods. Molnupiravir was locally available for prescription from 11 January 2022 in this hospital. The study period was from 11 January to 31 October 2022.

The COVID-19 Registry Japan of the National Centre for Global Health and Medicine was used for the present study with permission. The study data were collected and managed using Research Electronic Data Capture, a secure web-based data capture application hosted at the JCRAC data centre of the National Centre for Global Health and Medicine.

A standard dosage of 800 mg of molnupiravir was administered orally twice daily for 5 days. If oral intake was difficult, administration via nasogastric tube was attempted.

The following data were collected: patient characteristics, medical history, date of COVID-19 diagnosis, severity of COVID-19, date of initiation of treatment with molnupiravir, number of days of molnupiravir treatment, concomitant medications for the treatment of COVID-19, complete blood cell count tests at the initiation of treatment, adverse events, discontinuation rate, and 30-day mortality rate. The discontinuation rate of molnupiravir was calculated based on patients who were unable to complete 5 days of oral medication for any reason, including adverse events or worsening of their condition.

The severity of COVID-19 was recorded according to the Japanese Ministry of Health, Labour and Welfare (MHLW) criteria [8] and the National Institute of Allergy and Infectious Diseases Ordinal Scale (NIAID-OS) [9], while adverse events were assessed using the common terminology criteria for adverse events version 5.0 [10].

We assessed the outcome of patients with COVID-19 treated with molnupiravir according to the following criteria: (A) discontinuation rate of molnupiravir, (B) type, frequency, and severity of adverse events, and (C) all-cause mortality within 30 days of the diagnosis of COVID-19.

This study was approved by the National Hospital Organization Kyoto Medical Centre Review Board. (Approval number: 22–032) As this study was a retrospective cohort study, the informed consent form was not obtained from individual patients and an opt-out approach was used.

2.2. Statistical analysis

Categorical variables were compared using Pearson's chi-square test or Fisher's exact test, and continuous variables were compared using the Mann–Whitney U test. $P < 0.05$ was considered statistically significant. Categorical variables and continuous variables were reported as frequency (%) and median (range), respectively. All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA).

3. Results

We retrospectively analysed 102 patients who received molnupiravir for the treatment of COVID-19. All patients were diagnosed with COVID-19 using PCR. Forty-seven patients (46.1%) were aged ≥ 80 years (older patients), and 55 (53.9%) patients were aged < 80 years (younger patients). Ninety-seven of the 102 (95.1%) patients were hospitalized at the start of molnupiravir administration. Table 1 presents the characteristics of the study participants. The median ages of the older and younger patients were 86 and 68 years, respectively. There were no significant differences in coexisting diseases and history of vaccination for COVID-19 between older and younger patients. According to the

Table 1
Characteristics of the patients with COVID-19 treated with molnupiravir in this study.

	Older patients (≥ 80 years) $n = 47$	Younger patients (< 80 years) $n = 55$	P value
Age	86.0 (80.0–94.0)	68.0 (29.0–79.0)	–
Sex, (female)	21 (44.7)	20 (36.4)	0.393
Coexisting diseases			
Hypertension	20 (42.6)	27 (49.1)	0.509
Dyslipidaemia	9 (19.1)	14 (25.5)	0.447
Diabetes mellitus	16 (34.0)	16 (29.1)	0.591
COPD/Asthma	13 (27.7)	14 (25.5)	0.801
Malignancy	13 (27.7)	25 (45.5)	0.064
History of vaccination for COVID-19			
None	6 (12.8)	4 (7.3)	0.51
Full (≤ twice)	41 (87.2)	51 (92.7)	
Hospitalisation at the start of molnupiravir administration	47 (100)	50 (90.9)	
COVID-19 severity			
MHLW criteria			
Mild	26 (55.3)	44 (80.0)	0.015
Moderate 1	13 (27.7)	9 (16.4)	
Moderate 2	8 (17.0)	2 (3.6)	
Severe	0 (0.0)	0 (0.0)	
NIAID-OS criteria			
Grade 1	2 (4.3)	8 (14.5)	0.146
Grade 2	0 (0.0)	1 (1.8)	
Grade 3	0 (0.0)	1 (1.8)	
Grade 4	31 (66.0)	38 (69.1)	
Grade 5	11 (23.4)	5 (9.1)	
Grade 6	3 (6.4)	2 (3.6)	
Grade 7	0 (0.0)	0 (0.0)	
Blood cell counts before treatment			
White blood cell	6600 (2000–13,300)	4900 (2600–27,200)	0.074
Red blood cell ($\times 10^4$)	364.5 (223.0–481.0)	369.0 (201.0–533.0)	0.671
Haemoglobin, g/dL	11.6 (7.0–15.4)	11.2 (7.1–20.7)	0.855
Platelet ($\times 10^3$)	187.5 (89.0–502.0)	202.0 (92.0–649.0)	0.242

Data are shown as number (%) or median (range).
Abbreviations: COVID-19: coronavirus disease 2019, COPD: chronic obstructive pulmonary disease, MHLW: the Japanese Ministry of Health, Labour and Welfare, NIAID-OS: the National Institute of Allergy and Infectious Diseases Ordinal Scale.

severity index, older patients were significantly more likely to have moderate disease (moderate 1 and 2) according to the Japanese MHLW classification than younger patients. There were no significant differences between the two groups in terms of the NIAID-OS classification.

Table 2 shows the concomitant use of these drugs. In this study population, corticosteroids, sotrovimab, and tocilizumab were used concomitantly with molnupiravir. Corticosteroids were used in combination significantly more frequently in older patients than in younger patients (12.8% vs. 1.8%, $P = 0.046$). During the course of treatment, 8.5% of older patients and 1.8% of younger patients stopped taking molnupiravir, but there was no significant difference between the two groups. The reasons for discontinuation were worsening COVID-19 status in three patients and dysgeusia in two patients. Two of the five patients who discontinued molnupiravir died, one from exacerbation of COVID-19 and the other from exacerbation of a coexisting disease. Adverse events were observed in 39/102 (38.2%) patients. There were no significant differences in the occurrence of adverse events between the older and younger patients.

Table 3 shows the detailed profiles of the adverse events. A total of 47 adverse events were observed in 39 COVID-19 patients. The most common adverse events, in order of frequency, were diarrhoea (9.8%), exacerbation of coexisting diseases (6.9%), bone marrow suppression (6.9%), liver dysfunction (5.9%), and loss of appetite (4.9%). Of the 47 adverse events, 35 (74.5%) were minor, ranging from grades 1 to 3. Infection, exacerbation of coexisting diseases, and death were observed in 12 patients. However, there was no direct association between these adverse events and molnupiravir administration. The all-cause mortality rate was 11/102 (10.8%). The causes of death were exacerbation of pre-existing disease in seven patients, bacterial pneumonia in two patients, and exacerbation of COVID-19 in two patients. No molnupiravir-related deaths were observed.

4. Discussion

In the present study, we assessed the acceptability and safety of molnupiravir in older and younger patients. To date, few studies have evaluated the therapeutic effects of molnupiravir in the real world [11–13]. In this context, our study was conducted in the real world and focused on older patients aged ≥ 80 years to examine the acceptability and safety of molnupiravir. Various problems have emerged in COVID-19 practice in developed countries owing to the ageing of the population, and Japan is no exception [14]. One of the problems associated with an ageing population is the difficulty in using anti-COVID-19 drugs. Recently, it has recently been reported that remdesivir can be used relatively safely in older patients [15]. Oral antiviral agents may play an important role in the process of COVID-19 becoming a common disease. Whether they can be safely used in older patients is of interest to healthcare professionals. In terms of acceptability, the older patients had more discontinuations and failed to complete the prescribed number of days of dosing; however, the difference was not statistically significant.

Table 2
Profiles of treatment with molnupiravir and concomitant agents and adverse events.

	Older patients (≥ 80 years) $n = 47$	Younger patients (< 80 years) $n = 55$	P value
Concomitant use drugs			
Corticosteroids	6 (12.8)	1 (1.8)	0.046
Sotrovimab	3 (6.4)	5 (9.1)	0.723
Tocilizumab	1 (2.1)	0 (0.0)	0.461
Discontinuation of molnupiravir	4 (8.5)	1 (1.8)	0.178
Adverse events that occurred after the administration of molnupiravir	20 (42.6)	19 (34.5)	0.407

Data are shown as number (%).

Table 3
Type and severity of adverse events occurred after the administration of molnupiravir.

	Total (n = 102)	Older patients (≥ 80 years)	Younger patients (< 80 years)
Any adverse events	39 (38.2)	20 (42.6)	19 (34.5)
Liver dysfunction			
Any grade	6 (5.9)		
Grade 1	6	4	2
Renal dysfunction			
Any grade	3 (2.9)		
Grade 1	2	2	0
Grade 2	1	0	1
Vomiting			
Any grade	1 (0.98)		
Grade 2	1	0	1
Diarrhoea			
Any grade	10 (9.8)		
Grade 1	8	3	5
Grade 2	2	1	1
Appetite loss			
Any grade	5 (4.9)		
Grade 1	4	2	2
Grade 3	1	1	0
Dysgeusia			
Any grade	1 (0.98)		
Grade 2	1	0	1
Skin rash			
Any grade	1 (0.98)		
Grade 1	1	1	0
Infection			
Any grade	3 (2.9)		
Grade 3	1	1	0
Grade 5	2	0	2
Bone marrow suppression			
Any grade	7 (6.9)		
Grade 1	1	0	1
Grade 2	5	1	4
Grade 4	1	0	1
Exacerbation of coexisting diseases			
Any grade	7 (6.9)		
Grade 5	7	5	2
Exacerbation of COVID-19			
Any grade	3 (2.9)		
Grade 2	1	1	0
Grade 5	2	2	0

Data are shown as number (%). A total of 47 adverse events occurred in 39 patients.
Abbreviation: COVID-19: coronavirus disease 2019.

Three patients discontinued molnupiravir owing to worsening COVID-19.

In Japan, molnupiravir received regulatory approval in December 2021 and was not in use until early 2022. This was a time when the Omicron variant was predominant and antibody preparations became less effective and were almost no longer used as a treatment. The concomitant use of antiviral drugs is not recommended, and no other antiviral drugs are used in combination. Steroids are also not recommended for the treatment of mild disease. Therefore, only a few drugs were used in combination with molnupiravir during the study period.

There was no significant difference in the occurrence of adverse events between older and younger patients. The main adverse events were diarrhoea, bone marrow suppression, and exacerbation of coexisting diseases, but there were no differences in the frequency of occurrence or severity of any of them. Notably, exacerbations of coexisting diseases were seen in seven patients, all of whom died. Exacerbations of COVID-19 were also seen in three patients, two of whom died. This may be because of the high number of patients with advanced-stage malignancies as comorbidities, many of whom were terminally ill. No deaths were directly associated with molnupiravir administration.

All adverse events observed in this study were known adverse events described in the drug package insert, and no new adverse events were observed.

Our study suggests that molnupiravir can be safely administered to patients aged ≥ 80 years.

Many of the participants in the current study were hospitalised at the start of treatment, regardless of the severity of COVID-19. This is because of several reasons that are specific to Japan. At the time of this study, COVID-19 was a designated infectious disease, and, in principle, hospitalisation was promoted for the older individuals and those with underlying medical conditions. Our institution had a special ward dedicated to COVID-19 and provided medical care for hospitalised patients. Therefore, even patients with mild or moderate disease who were treated at our institution were, in principle, managed in hospital.

Oral antivirals were approved based on clinical trials conducted before the outbreak of the Omicron variant. Therefore, there was a concern that these drugs would not be sufficiently effective in the mainstream Omicron variant epidemics. A recent study from Hong Kong showed that even in an Omicron variant epidemic, molnupiravir contributes to a reduction in all-cause mortality and COVID-19 exacerbations after hospitalisation [16]. Another real-world study reported that even during an outbreak of Omicron strains, molnupiravir reduced mortality, with the effect being particularly pronounced in patients aged ≥ 80 years [13]. From these previous reports and our present study, it can be assumed that molnupiravir may be used for mild-to-moderate COVID-19, even in older patients. The pharmacokinetics and pharmacodynamics of molnupiravir are not affected by renal or hepatic function, which makes it easy to use in older patients.

This study had several limitations. Because this was a retrospective study conducted in a single medical centre, there may be gaps in the patient population compared with other regions and in the collection of data during the medical record review. In Japan, ritonavir-boosted nirmatrelvir and molnupiravir are drugs whose shipments are coordinated by the national government, and there were strong restrictions on their prescription during the study period. Therefore, it was not always used as indicated in the guidelines. It is possible that the restricted shipments of molnupiravir have resulted in inequitable distribution of medications to older patients eligible to receive them, and preferential distribution of medications to patients in better condition with a greater potential to benefit. This may lead to an underestimation of molnupiravir-related adverse events. In addition, COVID-19 is an infectious disease with ongoing treatment changes. Because treatment guidelines for COVID-19 changed over time, the recommendation for molnupiravir used differed over the course of the study period, and it is probable that different patients with the same severity of disease received different drugs at different times. The same drug may be used for different indications at different times; therefore, uniformity was not always maintained. This may have to an overestimation or underestimation of the acceptability and safety. Nevertheless, this study provides valuable data concerning older patients in the real world.

5. Conclusions

In conclusion, molnupiravir treatment is acceptable and safe in older patients with COVID-19 aged ≥ 80 years. Molnupiravir is an acceptable drug for use in older patients with COVID-19.

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Declaration of Competing Interest

We have no conflict of interest to declare.

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