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SEMINAR

Antiviral medications for mild-to-moderate COVID-19 in Japan: a gap of timing between clinical trials and real-world scenarios in a fast-changing pandemic

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ABSTRACT

The rapid spread of a novel type of coronavirus infection, coronavirus disease 2019 (COVID-19) has made it difficult to implement the results of clinical trials in real-world situations. After the emergence of the Omicron variant and messenger RNA vaccine, a combination of less virulent but more contagious viruses and more people with protective immunity has resulted in a larger number of patients with less severe, mild-to-moderate COVID-19. Many patients with severe conditions did not have extensive viral pneumonia frequently seen in the "pre-Omicron" era but had serious complications due to aggravation of underlying comorbidities or secondary bacterial infections. Most clinical trials for new antiviral drugs were conducted in the "pre-Omicron" period based on a different set of background patient characteristics than the ones seen in the Omicron period. Understanding situational differences due to the gap in the timing between clinical trials and the practical use of drugs for COVID-19 will assist in developing an effective treatment strategy in real-world practice. In this seminar, we reviewed antiviral treatments for mild-to-moderate COVID-19 from the viewpoint of the difference in patient backgrounds between clinical trials and real-world studies, focusing on drugs currently used in Japan.

KEY WORDS

COVID-19, clinical trials, real-world, Omicron variants, antiviral drugs

INTRODUCTION

In the past 3 years, coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) infection, first reported as a cluster of pneumonia cases in Wuhan, China [1], has altered its clinical picture because of the unbridled emergence of new variant strains and immunological modifications due to vaccination as well as previous infection.

During the pandemic of the earlier and more virulent "pre-Omicron" variants such as Alpha, Beta, and Delta strains, viral pneumonia superimposed by cytokine release syndrome resulted in severe acute respiratory distress syndrome in patients with risk factors for progression to severe disease [2]. However, in most instances, during the pandemic of less virulent but more contagious Omicron variants, patients became severely ill not because of viral pneumonia but because of secondary complications. These include aggravation of underlying medical problems or complications of an acute viral illness such as dehydration or concomitant bacterial infections, especially in elderly patients with multiple comorbidities [3].

In addition to these viral alterations, messenger RNA vaccines dramatically reduced the infection rate and the

incidence of severe cases [4]. As a result, a larger number of patients with mild-to-moderate SARS-CoV2 infection were hospitalized because of secondary complications. In this situation, the development of novel antiviral agents for mild-to-moderate COVID-19 is a critical strategy for preventing disease progression, hospitalization, and death.

However, the patient's background in a clinical trial of antiviral drugs may no longer be the same as that for the practical use of the drug. For example, a clinical trial of nirmatrelvir-ritonavir, a combination of oral protease inhibitors, was conducted between July and December, 2021 when the Delta variant was overwhelmingly dominant in the United States [5]. The clinical trial excluded patients who had received SARS-CoV-2 vaccines and those with previously confirmed infections. The difference in backgrounds between study patients in clinical trials and those in the real-world situations reminds us of the need for careful assessment of drug use and further observational studies with real-world data.

In this seminar, we reviewed antiviral drugs for mild-to-moderate COVID-19 from the perspective of the difference in patient's backgrounds between clinical trials and real-world studies, focusing on drugs currently used in Japan: remdesivir, molnupiravir, nirmatrelvir-ritonavir, and ensitrelvir.

TIMELINE OF KEY TRIALS, VARIANTS, AND VACCINATION

Since the first case in Japan was reported in Kanagawa Prefecture on January 16th [6], we have experienced several waves as the number of patients with COVID-19 rises and falls (**Fig. 1**). The detailed mechanism of wave formation is unknown, but is thought to be due to the combined effect of the emergence of new strains, human mobility control, and immunological status after infection or vaccination [7].

The first wave in Japan, after sporadic cases or clusters of the Wuhan strain and mainly composed of the European strain, peaked in April 2020, when the Japanese government declared a national state of emergency. The second and third waves, with strains of different lineages, peaked in July and December 2020, respectively. In June, 2021, the World Health Organization labeled the major variants of SARS-CoV-2 using the Greek alphabets [8]. The Alpha strains resulted in a 4th wave between March and May, 2021 and the Delta strain resulted in a 5th wave between July and September, 2021. After January, 2022, when the Omicron variant, a more transmissible but less virulent strain, started the 6th wave that lasted until June, 2022, waves were formed by each dominant Omicron subvariant, BA.1, BA.2 and BA.5 in the 6th, 7th, and 8th waves, respectively [9]. **Fig. 1** shows that there were a larger number of severe cases but a

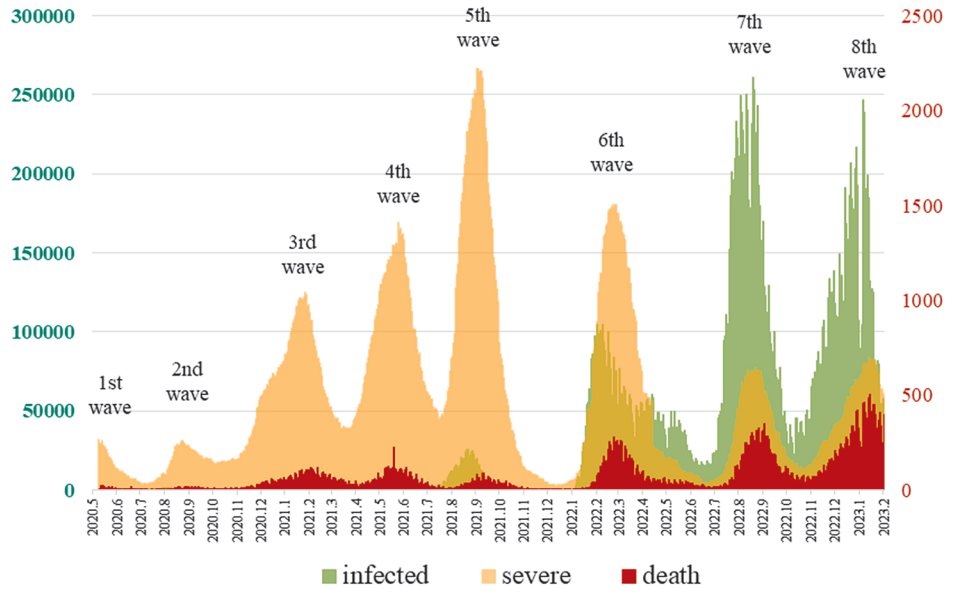

Fig. 1 A larger number of severe cases but a smaller number of infections and deaths were observed from the first to fifth waves, whereas a larger number of infections and deaths but a smaller number of severe cases were observed from the sixth to eighth waves

smaller number of infected cases and deaths from the first to fifth waves (the pre-Omicron period) compared to those from the sixth to eighth waves (the Omicron period). There were a larger number of infected cases and deaths but a smaller number of severe cases in the Omicron period than in the pre-Omicron period.

Fig. 2 shows the timeline of key clinical trials, variant strains, and vaccination statuses.

Remdesivir

Remdesivir, an inhibitor of viral RNA-dependent RNA polymerase [10], was formerly used in patients with moderate-to-severe hospitalized infections [11]. A randomized, double-blind, placebo-controlled trial for a 3-day course of remdesivir was conducted between September 18, 2020, and April 8, 2021, in the US, when the early strains, before the Alpha and Delta variants, were prevalent [12]. Patients were excluded from the study if they had previously received vaccination for COVID-19. In Japan, a 3-day course of remdesivir was officially approved and appended to product information in March, 2022, when the Omicron variant was the most dominant strain, and more than 80% of people had already received COVID-19 vaccine.

Molnupiravir

Molnupiravir, a ribonucleoside prodrug that inhibits SARS-CoV2 replication [10], was the first oral antiviral drug approved by the Japanese government in December, 2021.

The phase 3 component of a phase 2/3, double-blind, randomized, placebo-controlled trial for molnupiravir included patients enrolled between May 6 and October 2, 2021, when the Alpha and Delta variants were prevalent in the US [13]. In this trial, patients with prior SARS-CoV-2 vaccination were excluded. Molnupiravir obtained a fast-track approval in December 2021 and was included in the pharmaceutical price list of the National Health Insurance in September, 2022 in Japan. By the time it was widely used throughout the country, the major strain was the Omicron variant, and most people had received the SARS-CoV-2 vaccine.

Nirmatrelvir-ritonavir

Nirmatrelvir-ritonavir, nirmatrelvir packaged with ritonavir, is the second approved oral antiviral drug. Nirmatrelvir is an oral protease inhibitor and metabolized by cytochrome P450 (CYP) 3A4 [10]. Co-administration of ritonavir, a strong CYP3A4 inhibitor, is required to maintain the concentration of nirmatrelvir at a therapeutic level and enhance pharmacokinetics. A phase 2/3, double-blind, randomized, placebo-controlled trial enrolled patients at 343 sites worldwide between July 16 and December 9, 2021, when the Delta-variant was the dominant strain [13]. Patients who previously received the SARS-CoV-2 vaccine were excluded from

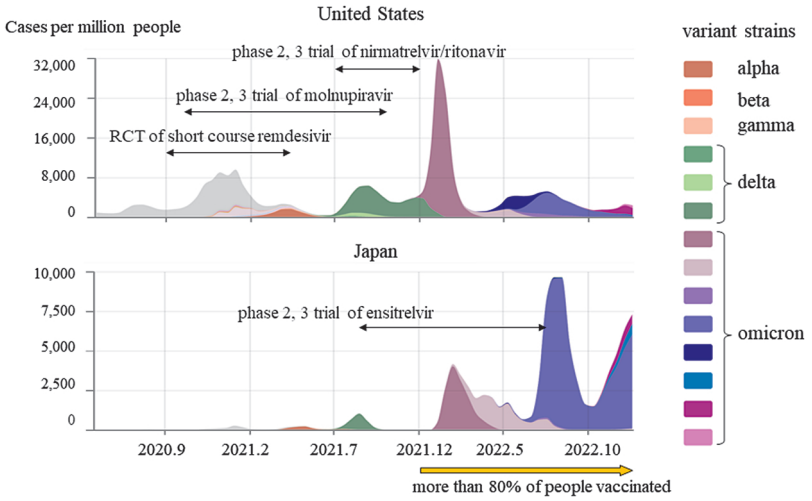

Fig. 2 The trials for remdesivir, molnupiravir, and nirmatrelvir/ritonavir were conducted in the pre-Omicron period with most study patients being vaccinated. The trial for ensitrelvir included patients who were vaccinated and infected with the Omicron variant

RCT: randomized control trial
modified from CoVariants (https://covariants.org/)

the trial. Nirmatrelvir-ritonavir was approved for use in Japan in February 2022, when the main variant had been almost completely replaced by the Omicron strain, and most people had received the SARS-CoV-2 vaccine.

Ensitrelvir

Ensitrelvir, a novel 3C-like protease inhibitor, is the first manufactured oral antiviral drug for mild-to-moderate COVID-19 in Japan [14]. Phases 2/3 of the study began in September 2021 and August, 2022. Phase 2b was conducted to investigate the improvement in major symptoms between January and February, 2022, when the Delta variant was replaced by the Omicron variant and most people had been vaccinated [15]. The data of the phase 3 component were used to analyze the outcome of symptom improvement [16]. As a result of phase 2b/3, ensitrelvir obtained emergency regulatory approval from the Japanese Ministry of Health, Labor, and Welfare in November, 2022.

REAL-WORLD EVIDENCE

Remdesivir (3-day administration)

Remdesivir, with a 10-day course of administration, was first proven to shorten recovery time in hospitalized patients with moderate-to-severe COVID-19 [11]. A phase 3 trial demonstrated that a 5-day course also had the same clinical benefits [17]. Given the hypothesis that the early administration of a short course of remdesivir would be effective for mild-to-moderate COVID-19 patients, a 3-day course of remdesivir was evaluated and found to be effective in the reduction of COVID-19 related hospitalization or death [12]. In a randomized controlled trial of 562 unvaccinated outpatients (≥12 years of age with at least one risk factor for progression to severe disease or ≥60 years of age) with mild-to-moderate COVID-19, initiation of a 3-day course of intravenous remdesivir (200 mg on day one and 100 mg on days two and three) within seven days of symptom onset reduced the risk of COVID-19 related hospitalization by 87 percent compared with placebo (hazard ratio [HR] 0.13, 95% confidence interval [CI] 0.03–0.59). The risk of all-cause hospitalization was also lower with remdesivir (HR 0.28, 95% CI 0.10–0.75). On day 28, no deaths were recorded in either group.

In the Omicron era, with more people being fully vaccinated, observational studies using real-world data were conducted in Mexico, Italy, and the US [18–20]. They showed that a short course of remdesivir significantly reduced the rates of death, hospitalization, and emergency department visits (**Table 1**). Patients in the studies in Mexico and the US had risk factors for progression to severe disease and patients in the study in Italy were the recipients of solid organ transplants.

Because remdesivir is a parenteral antiviral agent, patients were required to visit the outpatient department for three consecutive days. The requirement for frequent visits and infection control, including strict quarantine in an outpatient department, inevitably made outpatient treatment with remdesivir an unfeasible practice. In Japan, where most patients with risk factors are hospitalized, a 3-day course of remdesivir remains a major treatment option for hospitalized patients with mild-to-moderate COVID-19 who have risk factors for progression to severe disease [21].

This drug should be avoided in patients with renal dysfunction and an estimated glomerular filtration rate (eGFR) of <30 mL/min/1.73 m^2.

Molnupiravir

At the time of the interim analysis of the phase 3 trial, the proportion of patients needing hospitalization or dying by day 29 was 7.3% (28 of 385 patients) in the molnupiravir group and 14.1% (53 of 377 patients) in the control group. Molnupiravir reduced the number of hospitalized or dead patients by 51.8 %. However, in the final analysis, it reduced by only 30%; the proportion of patients needing hospitalization or dying by day 29 was 6.8% (48 of 709) in the molnupiravir group and 9.7% (68 of 699 patients) in the control group [13]. In an open-label, platform-adaptive, multicenter, randomized controlled trial conducted in the United Kingdom, molnupiravir failed to reduce hospitalization or death [22]. This study was conducted using non-hospitalized COVID-19 patients with ≥50 years of age or risk factors for progression to severe disease between December 2021 and April, 2022, when the dominant strain was the Omicron variant. Ninety-two percent of patients in the molnupiravir group and 93% in the control group received three vaccinations.

Three observational studies using large databases in Hong Kong in the Omicron era that evaluated ambulatory patients, hospitalized patients not requiring oxygen, and all patients with mild-to-moderate COVID-19 showed reduction of all-cause mortality (HR 0.48; 95% CI 0.40–0.59 [23], HR 0.76; 95% CI 0.61–0.95 [24], and HR 0.31; 95% CI 0.24–0.40 [25], respectively) (**Table 2**). In Japan, an observational study in Fukushima showed that molnupiravir prevented deterioration after hospital admission (adjusted odds ratio [OR], 0.448; 95% CI

Table 1 Observational studies for a short-course remdesivir

Authors	Participants	Design	Place	Period	Dominant strain	No. of patients	Vaccination status	Primary outcome	Reference
Rajme-López, Sandra et al.	mild-moderate Covid-19 patients with risk factors for progression to severe diseases	prospective cohort study	single center in Mexico	December 2021–April 2022	omicron	remdesivir: 54 control: 72	vaccinated at least twice remdesivir: 83.3% control: 76.4%	hospitalization or death aHR 0.16, 95% CI 0.06–0.44	18
Colaneri, Marta et al.	recipients of solid organ transplant with mild-moderate Covid-19	prospective cohort study	single center in Italy	December 2021–April 2022	omicron	remdesivir: 7 control: 17	vaccinated at least twice remdesivir: 57.1% control: 94.1%	hospitalization aHR 0.05, 95% CI 0.00–0.65	19
Piccicacco, Nicholas et al.	mild-moderate Covid-19 patients with risk factors for progression to severe diseases	retrospective cohort study	singe ambulatory infusion clinic in US	December 2021–February 2022	omicron	remdesivir: 82 control: 90	vaccinated at least twice remdesivir: 43.9% control: 35.6%	hospitalization and/or ED visit OR 0.41 95% CI 0.17–0.95	20

aHR = adjusted hazard ratio, CI = confidence interval, OR = odds ratio

0.206–0.973) but failed to show a reduction in all-cause mortality [26] (**Table 2**).

Despite the mixed results of clinical trials and observational studies, molnupiravir has been approved for use in Japan and is now the most commonly used oral antiviral drug because of its favorable safety profile compared to that of nirmatrelvir/ritonavir, which interacts with many drugs. This drug can be safely administered to patients with renal dysfunction. Currently, molnupiravir should be prescribed for mild-to-moderate COVID-19 ambulatory patients with risk factors for progression to severe disease or for patients not requiring oxygen in facilities (e.g., nursing care facilities) when patients have contraindications to nirmatrelvir/ritonavir.

Nirmatrelvir/Ritonavir

Currently, nirmatrelvir/ritonavir is the most successful oral antiviral drug in terms of efficacy and mortality reduction in both clinical trials and observational studies using real-world data. A phase 2/3 double-blind, randomized, controlled trial for mild-to-moderate unvaccinated patients with COVID-19 who had risk factors for progression to severe disease showed an 89.1% reduction in the incidence of COVID-19–related hospitalization or death in the nirmatrelvir/ritonavir group compared to the placebo group [22–24, 26–28]. Six major observational studies were conducted in the Omicron era, with a significant number of people fully vaccinated (**Table 3**) [23–25, 27–29]. All the studies showed a significant reduction in all-cause mortality. Therefore, national guidelines in many countries recommend nirmatrelvir/ritonavir as the first-line drug for mild-to-moderate COVID-19 patients with risk factors for progression to severe disease.

Drug interactions between ritonavir and many medicines have had a large negative impact on its widespread use. Ritonavir, a strong CYP3A4 inhibitor, prevents the rapid metabolism of nirmatrelvir by CYP3A4 and helps to maintain its concentration at a therapeutic level.

According to the Infectious Disease Society of America guidelines, among the top 100 drugs, rivaroxaban and salmeterol interact so severely that nirmatrelvir/ritonavir cannot be used concomitantly [30].

In addition, this drug should be avoided in patients with an eGFR less than 30 mL/min/1.73 m^2.

Ensitrelvir

In a trial of a novel oral antiviral drug, ensitrelvir, manufactured by the Japanese pharmaceutical company Shionogi & Co., Ltd., unique definitions of study participants

Table 2 Observational studies for molnupiravir

Authors	Participants	Design	Place	Period	Dominant strain	No. of patients	Vaccination status	Primary outcome	Reference
Suzuki, Yasuhito et al.	mild-moderate COVID-19 patients with risk factors for progression to severe diseases	retrospective cohort study	multicenter in Fukushima, Japan	January–April, 2022	omicron	molnupiravir: 230 control: 690 (after propensity score matching)	vaccinated at least twice molnupiravir: 81.7% control: 82.2%	any deterioration aOR 0.448, 95% CI 0.206–0.973 all-cause death no significant difference (effect size not shown)	26
Wong, Carlos K H et al.	hospitalized patients not requiring oxygen therapy on admission	retrospective cohort study	database of Hospital Authority, the Department of Health, and the Hong Kong Death Registry	February–April, 2022	omicron	molnupiravir: 1,856 control: 1,856 (after propensity score matching)	vaccinated at least twice molnupiravirr: 6.2% control: 9.0%	all-cause mortality HR 0.48, 95% CI 0.40–0.59	23
Wong, Carlos K H et al.	ambulatory mild to moderate Covid-19 patients with risk of progressing to severe disease	retrospective cohort study	public inpatient and outpatient services in Hong Kong	February–June, 2022	omicron	molnupiravir: 4983 control: 49234	vaccinated at least twice molnupiravir: 16.1% control: 33.2%	all-cause mortality HR 0.76, 95% CI 0.61–0.95 hospitalisation HR 0.98, 95% CI 0.89–1.06 In-hospital disease progression HR 0.57, 95% CI 0.43–0.79	24
Wai, Abraham Ka-Chung et al.	mild to moderate COVID-19 patients risk factors for progression to severe diseases	retrospective cohort study	database of Hospital Authority, Hong Kong	February–March, 2022	omicron	molnupiravir: 20,224 control: 20,057	data not available 82.6% of population vaccinated twice	28-day all-cause mortality HR 0.31, 95% CI 0.24–0.40	25

HR = hazard ratio, CI = confidence interval, aOR = adjusted odds ratio

Table 3 **Observational studies for nirmatrelvir/ritonavir**

Authors	Participants	Design	Place/Database	Period	Dominant strain	No. of patients	Primary outcome	Reference
Ganatra, Sarju et al.	non-hospitalized vaccinated patients	retrospective cohort study	database of a global health research network	December 2021–April 2022	omicron	nirmatrelvir/ritonavir: 1,130 control: 1,130 (after propensity score matching)	composite of all-cause ER visits, hospitalization, or death in 30 days OR 0.507, 95% CI 0.39–0.67	27
Najjar-Debbiny, Ronza et al.	non-hospitalized patients with risk factors for progression to severe diseases	retrospective cohort study	database of the largest healthcare provider in Israel and the Israeli Ministry of Health COVID-19 database	January–February 2022	omicron	nirmatrelvir/ritonavir: 4,737 control: 175,614	severe COVID-19 aHR 0.54, 0.39–0.75 mortality aHR 0.20, 95% CI 0.17–0.22	28
Arbel, Ronen et al.	non-hospitalized adult patients with risk factors for progression to severe diseases	retrospective cohort study	database of the largest healthcare provider in Israel	January–February 2022	omicron	nirmatrelvir/ritonavir: 3,902 control: 105,352	hospitalization aHR 0.27, 95% CI 0.15–0.49 death aHR 0.21, 95% CI 0.05–0.82 (patients >=65 years)	29
Wong, Carlos K H et al.	hospitalized patients not requiring oxygen therapy on admission	retrospective cohort study	database of Hospital Authority, the Department of Health, and the Hong Kong Death Registry	February–April, 2022	omicron	nirmatrelvir/ritonavir: 890 control: 890 (after propensity score matching)	all-cause mortality HR 0.34, 95% CI 0.23–0.50	23
Wai, Abraham Ka-Chung et al.	mild to moderate COVID-19 patients risk factors for progression to severe diseases	retrospective cohort study	database of Hospital Authority, Hong Kong	February–March, 2022	omicron	nirmatrelvir/ritonavir: 18,951 control: 20,057	28-day all-cause mortality HR 0.10, 95% CI 0.05–0.21	25
Wong, Carlos K H et al.	ambulatory mild to moderate Covid-19 patients with risk of progressing to severe disease	retrospective cohort study	public inpatient and outpatient services in Hong Kong	February–June, 2022	omicron	nirmatrelvir/ritonavir: 5,542 control: 54,672	all-cause mortality HR 0.34, 95% CI 0.22–0.52 hospitalization HR 0.76, 95% CI 0.67–0.86 In-hospital disease progression HR 0.57, 95% CI 0.38–0.87	24

aHR = adjusted hazard ratio, CI = confidence interval, OR = odds ratio

and outcome measures were used. Unlike trials for other antiviral drugs, this study included patients with COVID-19 regardless of the risk factors for severe disease and prior vaccination. Clinical outcomes were not defined as a consequence of severe disease, such as mortality or hospital admission, but rather as symptom improvement.

In the phase 2b component of the phase 2/3 randomized control trial, patients were randomly classified into ensitrelvir 125 mg, ensitrelvir 250 mg, or placebo groups [15]. Two primary outcomes, virological and clinical, were established. The virological outcome was the change in SARS-CoV2 viral titer, and the clinical outcome was the change in the time-weighted average of the total score of predefined 12 COVID-19 symptoms: 1. Stuffy or runny nose, 2. Sore throat, 3. Shortness of breath (difficulty breathing), 4. Cough, 5. Low energy or tiredness, 6. Muscle or body aches, 7. Headache, 8. Chills or shivering, 9. Feeling hot or feverish, 10. Nausea (feeling like you want to throw up), 11. Vomiting (throwing up), and 12. Diarrhea (loose or watery stools).

The change in viral titers from baseline to day 4 was significantly greater with ensitrelvir 125 mg and 250 mg than with the placebo. However, in the time-weighted average change in the total score of the 12 COVID-19 symptoms from baseline to 120 hours, no significant difference was observed between the ensitrelvir and placebo groups.

A post hoc analysis was performed, and the mean change from the baseline in the composite score of four respiratory symptoms and one feverishness symptom was found to be greater in the ensitrelvir group than in the placebo group: stuffy or runny nose, sore throat, shortness of breath (difficulty breathing), cough, feeling hot, or feverish. Preliminary analysis using the data of the early part of the phase 3 component showed that the median time for improvement of these five symptoms was significantly 1.2-day shorter in the ensitrelvir 125 mg group than in the placebo group (6.8 days vs. 8.0 days, $p = 0.04$) [16, 31].

In response to the result of the 2b/3 phase trial, the Japanese government granted fast-track approval for its use in November 2022. This approval aroused controversies among clinicians due to the fact that the result of the post hoc analysis was adopted after the analysis with predefined outcomes did not show favorable results.

As long as the trial includes patients without risk factors for severe disease and the outcome does not include mortality or hospital admission, this drug should not be used in patients with risk factors for disease progression to death or serious clinical consequences. It should be used for patients with no risk factors based on discussions with patients about the risks, benefits, and costs of a 1.2-day shortening of symptoms.

This drug can be used for patients with renal dysfunction unless they take colchicine.

CONCLUSION

In the era of COVID-19 pandemic, with the dominance of less virulent but more contagious Omicron variant and with dissemination of vaccination, antiviral drugs for mild-to-moderate COVID-19 are central in treatment. Currently, short-course parenteral remdesivir should be used for hospitalized patients, and nirmatrelvir/ritonavir for ambulatory patients with risk factors for progression to severe disease. When patients have contraindications for nirmatrelvir/ritonavir, molnupiravir can be used as an alternative. The role of ensitrelvir, a novel drug is yet to be established.

In the fast-changing pandemic of acute infectious diseases such as COVID-19, the situation during a clinical trial for a new drug is not the same as when the drug is used in the real-world. Clinicians should understand the differences between situations when a drug is developed and when it is used.

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