Original Article

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Efficacy and safety of sotrovimab for vaccinated or unvaccinated patients with mild-to-moderate COVID-19 in the omicron era

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SUMMARY Although sotrovimab, one of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) neutralizing antibodies has been shown to be effective in patients with mild-to-moderate coronavirus disease 2019 (COVID-19) with risk factors, their efficacy in mRNA COVID-19 vaccinated patients in omicron era is unknown. To evaluate the effectiveness of sotrovimab clinical data from both COVID-19 vaccinated and unvaccinated patients who were hospitalized and receiving sotrovimab at the Japanese Red Cross Medical Center were compared. The efficacy and adverse events were evaluated. Of the total 60 patients enrolled in this study, 45 had received the mRNA COVID-19 vaccine and 15 were unvaccinated. The clinical progression with low nasal cannula or face mask was not significantly different between groups (occurring in one patient in each group; $p = 0.44$), with no further progression in both groups. The duration of hospitalization was eight days for both groups ($p = 0.90$). Two patients in each group experienced adverse events (7%, $p = 0.26$). The results suggested that the efficacy and safety of sotrovimab against mild-to-moderate COVID-19 with risk factors in the omicron era might not be different regardless of the vaccination status. The results of the present study are encouraging; however, further randomized clinical studies are needed.

Keywords COVID-19, severe acute respiratory syndrome coronavirus 2, adverse event, efficacy, neutralizing antibodies

1. Introduction

The number of people infected with coronavirus disease 2019 (COVID-19) is increasing worldwide (*1*). The number of COVID-19 patients is increasing in Japan as well, and infection control and medical care are essential. From July 2021, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-neutralizing antibody therapeutics and oral drugs were approved for use in patients with COVID-19 with risk factors (*2*). SARS-CoV-2-neutralizing antibodies and oral drugs are therapies used for mild-to-moderate cases, and SARS-CoV-2-neutralizing antibodies are said to be particularly effective against mild-to-moderate COVID-19 with risk factors (*3*). Two SARS-CoV-2-neutralizing antibodies, REGN-COV2 (Regeneron Pharmaceuticals, Inc., USA) and sotrovimab (VIR-7831; Vir Biotechnology and GlaxoSmithKline, United Kingdom), are available in Japan (*4-6*). However, the omicron variant became prevalent in Japan in January 2022, and it is said that the effect of REGN-COV2 on the omicron strain is diminished (*2*). Therefore, sotrovimab became the antibody drug of choice. However, during clinical trials of sotrovimab, only patients unvaccinated against COVID-19 were included as target patients, and the efficacy and safety of sotrovimab in vaccinated patients remains unknown (*5*). Therefore, we investigated the efficacy and safety of sotrovimab in the omicron era for patients with COVID-19 with risk factors, and compared the results between patients who were vaccinated or unvaccinated against COVID-19.

2. Materials and Methods

2.1. Eligibility criteria

Patients diagnosed with COVID-19 and admitted to the Japanese Red Cross Medical Center were screened for the analysis. In accordance with the National Institutes of Health classification criteria, patients with COVID-19 were classified into four categories as follows: 1) mild illness group, which included patients with different signs and symptoms of COVID-19 excluding shortness of breath, dyspnea, or abnormal chest imaging finding;

2) moderate illness group, which included patients with lower respiratory diseases diagnosed based on clinical assessment or imaging examination and a blood oxygen saturation level (SpO_2) ≥ 94% on room air at sea level; 3) severe illness group, which included patients with respiratory rate > 30 breaths per minute, SpO_2 < 94% on room air at sea level, arterial partial pressure of oxygen to fraction of inspired oxygen ratio < 300 Torr, or lung infiltrates > 50%; and 4) critical illness group, which included patients with respiratory failure, septic shock, and/or multi-organ dysfunction (*7*).

From January 2022 to February 2022 of the omicron era, patients who demonstrated mild or moderate illness with COVID-19 risk factors on admission and who received sotrovimab were consecutively enrolled in this study. Patients with a compatible symptom onset no more than seven days before the administration and who had at least one of the following risk factors: age ≥ 55 years; body mass index (BMI) ≥ 30 kg/m^2; or comorbidity with diabetes, chronic kidney disease (estimated glomerular filtration rate, < 60 mL per minute per 1.73 m^2 of body-surface area) including hemodialysis, congestive heart failure (New York Heart Association class II, III, or IV), cancer, chronic obstructive pulmonary disease, moderate-to-severe asthma, hypertension, hyperlipidemia, pregnancy, or long term use of steroids or immunosuppressants were included in the study.

2.2. Procedures

Consecutive patients received a single 500 mg, 30 minutes infusion of sotrovimab on the day of, or the day after, admission. This study did not mandate any treatment for COVID-19 other than sotrovimab; as a result, the patients received another treatment at the discretion of their physicians according to the local standard of care if the patient's condition worsened.

2.3. COVID-19 vaccines

Two kinds of mRNA vaccines (*8*); mRNA-1273 (developed by Moderna Ltd., USA) and BNT162b (developed by Pfizer and BioNTech Ltd., USA) were the first vaccines approved for emergency use in Japan. In this study, patients who had received at least two doses of either of these vaccines were defined as the vaccinated group, and those who had not received either of these vaccines were defined as the unvaccinated group.

2.4. Statistical analyses

All data are presented as medians with interquartile ranges (IQRs) or absolute numbers with percentages. The Fischer exact test was used for categorical data, and the Mann-Whitney *U* test was used for numeric data to evaluate the difference between the vaccinated and unvaccinated groups. *P*-values < 0.05 were considered significant. Data were analyzed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan; *http://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmed.html*), a graphical user interface for R software (version 2.13.0; The R Project for Statistical Computing; *http://www.r-project.org*) and a modified version of R Commander (*9*). Adverse events were reported in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

2.5. Ethics approval and consent to participate

This study was approved by the Ethics Committee for Clinical Studies of the Japanese Red Cross Medical Center (No. 1394; April 28, 2022). Written informed consent for the use of sotrovimab was obtained from all patients. Additional informed consent for this study was waived owing to the nature of the study design, which involved retrospective chart review to obtain clinical information. In accordance with the Japanese ethical guidelines for clinical research, the need for informed consent was waived.

3. Results

In total, 60 patients with mild or moderate COVID-19 who received sotrovimab were enrolled in this study. Of the 60 patients, 43 had received two doses of mRNA COVID-19 vaccine, two had received three doses of mRNA COVID-19 vaccine, and 15 had never received any mRNA COVID-19 vaccine. Thus, 45 patients were enrolled in the vaccinated group and 15 in the unvaccinated group. Details on whether the mRNA COVID-19 vaccine ingested was mRNA-1273 or BNT162b were not available. The clinical characteristics of the patients on admission are presented in Table 1. Briefly, the median patient age was 67 years (IQR: 53-79 years), and 36 patients (60%) were male. Regarding concurrent risk factors, 17 (28%) patients had one, 18 (30%) patients had two, and 26 (42%) patients had three or more. At admission, 46 patients (77%) were diagnosed with mild symptoms and 14 (23%) with moderate symptoms. There was no significant difference in baseline admission data between the vaccinated and unvaccinated groups.

The patient outcomes are presented in Table 2. One patient in each group experienced severe or critical progression (p = 0.44). Both groups had one patient requiring a low nasal cannula or face mask, but they had no further progression. The median duration of hospitalization was 8 days (interquartile range [IQR]: 6-10 days) for both groups, with no significant difference (p = 0.90).

The adverse events are presented in Table 3 and were reported in accordance with CTCAE version 5.0. Adverse events occurred in a total of four patients (7%),

Table 1. Clinical characteristics of the patients on admission

Characteristic	Overall (n = 60)	Vaccinated (n = 45)	Unvaccinated (n = 15)	p value
Age, years (IQR)	67 (53-79)	70 (54-83)	64 (46-70)	0.1
Male sex-No. (%)	36 (60)	27 (60)	9 (60)	1.0
BMI, kg/m^2 (IQR)	22.8 (19.8-26.2)	22.8 (19.6-26.1)	23.5 (20.3-25.7)	0.98
Any risk factor	60 (100)	45 (100)	15 (100)	
Age ≥ 55 years (%)	43 (72)	32 (71)	11 (73)	1.0
Obesity: BMI ≥ 30 (%)	3 (5)	2 (4)	1 (6)	1.0
Diabetes (%)	15 (25)	12 (27)	3 (20)	0.70
Chronic kidney disease (%)	9 (15)	5 (11)	4 (27)	0.21
Congestive heart failure (%)	6 (10)	5 (11)	1 (6)	1.0
Cancer (%)	8 (13)	6 (13)	2 (13)	1.0
Chronic obstructive pulmonary disease (%)	2 (3)	2 (4)	0 (0)	1.0
Moderate-to-severe asthma (%)	4 (7)	4 (9)	0 (0)	0.56
Hypertension (%)	23 (38)	16 (36)	7 (47)	0.54
Hyperlipidemia (%)	13 (22)	8 (18)	5 (33)	0.28
Pregnancy (%)	3 (5)	1 (2)	2 (13)	0.15
Long term use of steroids or immunosuppressants (%)	3 (5)	3 (7)	0 (0)	0.57
No. of concurrent risk factors (%)				0.51
1	17 (28)	13 (29)	4 (27)	
2	18 (30)	15 (33)	3 (20)	
≥3	25 (42)	17 (38)	8 (53)	
Severity on admission (%)				0.73
Mild	46 (77)	35 (78)	11 (73)	
Moderate	14 (23)	10 (22)	4 (27)	

IQR, interquartile range; BMI, Body Mass Index.

Table 2. Patient outcomes

Outcome	Overall (n = 60)	Vaccinated (n = 45)	Unvaccinated (n = 15)	p value
Primary outcome				
Severe or critical progression, No. (%)	2 (3)	1 (2)	1 (7)	0.44
Low flow nasal cannula or face mask	2 (3)	1 (2)	1 (7)	
High flow nasal cannula or noninvasive mechanical ventilation	0 (0)	0 (0)	0 (0)	
Intensive mechanical ventilation	0 (0)	0 (0)	0 (0)	
Admission to ICU for any cause	0 (0)	0 (0)	0 (0)	
Death from any cause	0 (0)	0 (0)	0 (0)	
Secondary outcome				
Duration of hospitalization, days (IQR)	8 (6-10)	8 (6-10)	8 (6-10)	0.90

ICU, intensive care unit; IQR, interquartile range.

Table 3. Adverse events

Event	Overall (n = 60)	Vaccinated (n = 45)	Unvaccinated (n = 15)	p value
All adverse events, No. (%)	4 (7)	2 (4)	2 (14)	0.26
Infusion-related reactions, No. (%)	1 (2)	1 (2)	0 (0)	
Post-dose fever, No. (%)	2 (3)	1 (2)	1 (7)	
Liver dysfunction, No. (%)	1 (2)	0 (0)	1 (7)	

wherein infusion-related reactions occurred in 2% of patients, post-dose fever in 3%, and liver dysfunction in 2%. There were no significant differences between the two groups (p = 0.26).

4. Discussion

To the best of our knowledge, this is the first report to investigate the efficacy and safety of sotrovimab for patients with mild-to-moderate COVID-19 with risk factors in the omicron era according to their vaccination status.

COVID-19 is an infection caused by SARS-CoV-2 (*1*). In patients with severe disease, excessive inflammation and cytokine storm-like conditions are considered serious; therefore, anti-inflammation and antiviral drug combination therapies are currently being used for patients with severe COVID-19 (*10*). However, early intervention is necessary for patients with risk factors to improve the efficacy of COVID-19 therapy (*3*).

The clinical trial of sotrovimab for mild-to-

moderate COVID-19 included 583 patients (291 in the sotrovimab group and 292 in the placebo group) (*5*). That study reported that three patients (1%) in the sotrovimab group and 21 patients (7%) in the placebo group had disease progression leading to hospitalization or death, with sotrovimab significantly reducing disease progression compared to that in the placebo group. The placebo group also reported five intensive care unit admissions, including one death by day 29. Safety was evaluated in 868 patients (430 in the sotrovimab group and 438 in the placebo group); 17% and 19% of the individuals in the sotrovimab and placebo groups, respectively, reported adverse events, with serious adverse events occurring rather less frequently in the sotrovimab group than in the placebo group. Based on these results, the investigators reported that sotrovimab reduced the risk of disease progression in patients with mild-to-moderate Covid-19 with risk factors and had no safety problems.

In the present study, sotrovimab was found to be highly effective, with only a 3% (2 out of 60 patients) clinical progression rate, and no patients required invasive mechanical ventilation or admission to the intensive care unit (ICU). In addition, these effects were not significantly different between the vaccinated and unvaccinated groups, suggesting that sotrovimab could be effective in vaccinated COVID-19 patients with risk factors. Although two sotrovimab-treated patients had progression requiring low flow nasal oxygenation, both patients had improvement with remdesivir and steroid therapies.

The incidence of adverse events was 7%. All adverse events were grade 2 in CTCAE, and no serious adverse events occurred with or without mRNA COVID-19 vaccination. This result suggests that sotrovimab can be safely used with or without mRNA COVID-19 vaccination.

The present study had several limitations. First, the study was conducted at a single center, and only a few patients were included. Second, it was unknown whether patients in the vaccination group received mRNA-1273 or BNT162b vaccine and the duration since vaccination. Third, the COVID-19 variant of all enrolled patients has not been determined, although it is thought to have largely replaced the omicron variant in Japan since January 2022. Further investigations are needed to clarify this aspect.

In conclusion, this study suggested that the efficacy and safety of sotrovimab against mild-to-moderate COVID-19 with risk factors in the omicron era might not be different regardless of the vaccination status. The results of this study are promising because the clinical impact of the neutralizing antibody might be also significant in mild-to-moderate COVID-19 patients with risk factors vaccinated with mRNA COVID-19, although further randomized clinical trials must be conducted to confirm these findings.

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