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Note

Clinical efficacy of casirivimab-imdevimab antibody combination treatment in patients with COVID-19 Delta variant

Naoyuki Miyashita [a,*], Yasushi Nakamori [b], Makoto Ogata [a], Naoki Fukuda [a], Akihisa Yamura [a], Yoshihisa Ishiura [c]

[a] First Department of Internal Medicine, Division of Respiratory Medicine, Infectious Disease and Allergology, Kansai Medical University, Japan
[b] Department of Emergency Medicine, Kansai Medical University Medical Center, Japan
[c] First Department of Internal Medicine, Division of Respiratory Medicine, Oncology and Allergology, Kansai Medical University Medical Center, Japan

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ABSTRACT

Introduction: Casirivimab-imdevimab, an antibody cocktail containing two severe acute respiratory syndrome coronavirus 2 neutralizing antibodies, reduces the viral load and the risk of coronavirus disease 2019 (COVID-19)-related hospitalization or death. The objective of this study was to evaluate the clinical efficacy of casirivimab-imdevimab in patients with COVID-19 Delta variant in Japan.

Methods: This study was conducted at five institutions and assessed a total of 461 patients with COVID-19 who met the inclusion criteria. The treatment group received a dose of casirivimab-imdevimab consisting of a cocktail of two monoclonal antibodies, (casirivimab 600 mg and imdevimab 600 mg intravenously). The control consisted of age- and sex-matched COVID-19 patients (n = 461) who sufficed the inclusion criteria but did not receive casirivimab-imdevimab. The outcome was the requirement of oxygen therapy.

Results: In the treatment group, patients received oxygen therapy (n = 30), nasal canula (n = 23), high flow nasal cannula (n = 5), and mechanical ventilation (n = 2). In the control group, patients received oxygen therapy (n = 56), nasal canula (n = 45), high flow nasal cannula (n = 8), and mechanical ventilation (n = 3). The administration of oxygen therapy was significantly lower in the treatment group than the control group (6.5% vs. 12.1%, P = 0.0044). All these patients admitted to our hospitals and received additional therapy and recovered.

Conclusions: Our results demonstrate that the casirivimab-imdevimab combination antibody treatment is associated with reduced rates of requiring oxygen therapy among high-risk patients with COVID-19 Delta variant.

The novel coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) first emerged in December 2019, when a cluster of patients with pneumonia of unknown cause was recognized in Wuhan, China [1]. The spread of the virus was rapid and currently COVID-19 cases are present worldwide. SARS-CoV-2 can be spread by asymptomatic, pre-symptomatic, and symptomatic carriers. The optimal approach to treatment of COVID-19 is evolving. Randomized controlled trial data suggest a mortality benefit with corticosteroids as well as with tocilizumab or baricitinib and a possible clinical benefit with remdesivir [2–5]. Based on the pathogenesis of COVID-19, approaches that target the virus itself are more likely to work early in the course of infection.

Casirivimab-imdevimab, an antibody cocktail containing two SARS-CoV-2 neutralizing antibodies, reduces the viral load and the risk of COVID-19-related hospitalization or death from any cause, and resolves symptoms [6–9]. Subcutaneous casirivimab-imdevimab prevented symptomatic COVID-19 and asymptomatic SARS-CoV-2 infection in previously uninfected household contacts of infected persons [10], and reduced the incidence of symptomatic COVID-19 over 28 days in infected household contacts [11].

Casirivimab-imdevimab was approved by the ministry of health and labor of Japan as a special occasion on July 2021, to prevent a severe form of the infection with hypoxia. From June 2021, a new lineage of SARS-CoV-2, the Delta (B.1.617.2) variant, spread rapidly throughout Japan, and there was 100% replacement of previous variants by the Delta variant by July 2021. The clinical efficacy of casirivimab-imdevimab combination antibody treatment with large sample size has not been investigated in settings of Japan. This study evaluated the clinical efficacy of casirivimab-imdevimab in patients with COVID-19 Delta variant in Japan.

* Corresponding author. First Department of Internal Medicine, Division of Respiratory Medicine, Infectious Disease and Allergology, Kansai Medical University, 2-3-1 Shin-machi, Hirakata, Osaka, 573-1191, Japan.
E-mail address: miyashin@hirakata.kmu.ac.jp (N. Miyashita).

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Abbreviations

COVID-19 Coronavirus disease 2019
RT-PCR Reverse transcription polymerase chain reaction
SARS-CoV-2 Severe acute respiratory syndrome coronavirus 2

The present study was conducted at five institutions (Kansai Medical University Hospital, Kansai Medical University Medical Center, Kansai Medical University Kori Hospital, Kansai Medical University Kuzuha Hospital, and Kansai Medical University Temmabashi General Clinic) between July 2021 and December 2021, and assessed a total of 461 patients with COVID-19. The following inclusion criteria, based on the package insert, were used to administer casirivimab-imdevimab: 1) positive SARS-CoV-2 antigen or polymerase chain reaction (PCR) tests of specimens taken from nasopharyngeal area within 72 h prior to enrollment, 2) compatible symptoms onset of no more than 7 days before administration, 3) oxygen saturation level at room air of more than 93%, and 4) the patient has at least one of the risk factors shown in Table 1. (https://www.info.pmda.go.jp/go/pack/62505A0A1023_1_01/). Applicants with casirivimab-imdevimab are introduced and consulted to our hospitals from Follow-up Center in Osaka prefecture. The intravenous drip of casirivimab-imdevimab was done in short-term hospitalization for first two weeks to observe side effect. After that the intravenous drip was done in the outpatient department except for patients with low oxygen. In addition, we visited to the accommodation medical facility (hotel recuperation) of COVID-19 for the intravenous drip at the request of the health center. The treatment group received a dose of casirivimab-imdevimab consisting of a cocktail of two monoclonal antibodies, (casirivimab 600 mg and imdevimab 600 mg intravenously).

We visited the accommodation medical facility of COVID-19 every day for provide medical care. Thus, we selected the patients recuperating in the accommodation medical facility as controls who sufficed the inclusion criteria but did not receive casirivimab-imdevimab. The main reason why patients does not want to be treated was anxiety about side effects. During the study period, there were 548 controls with median age of 48 years and 262 males. Most common risk factor was *age* ≥50 years old (n = 291), next to smoking history (n = 202), cardiovascular diseases including hypertension (n = 126), obesity with body mass index ≥30 kg/m^2 (n = 122), diabetes mellitus either type 1 or 2 (n = 89), hyperlipidemia (n = 74), chronic lung diseases including asthma (n = 63), chronic kidney disease including those on hemodialysis (n = 19), chronic liver failure (n = 17), immunosuppressed status including those on chemotherapy, organ transplants, poorly controlled human immunodeficiency virus infection, sickle cell anemia, thalassemia and long term use of immunosuppressive medication (n = 15) and late pregnancy (n = 15). Finally, we enrolled the 461 controls consisted of age- and sex-matched COVID-19 patients. Informed consent was obtained from all patients, and the study protocol was approved by the Ethics Committee of Kansai Medical University (approval number 2020319).

The outcome was the requirement of oxygen therapy (either nasal canula, high flow nasal cannula (HFNC) oxygenation, or mechanical ventilation). We used Wilcoxon rank sum test for continuous variables, and Fisher's exact test for categorical variables.

The characteristics of the treatment and the control groups are shown in Table 1. The treatment patients received casirivimab-imdevimab as outpatients (n = 289), as inpatients (n = 76), and at an accommodation medical facility (n = 96). Eighty-five patients had been vaccinated *(*BNT162b2 or mRNA-1273) against SARS-CoV-2, of which 71 patients had received one dose and 14 patients received two doses. Median time from symptom onset to treatment was four days. In contrast, median time from symptom onset to informed consent of treatment in control group was three days. There were no significant differences between the two groups for one risk factor.

In the treatment group, patients received oxygen therapy (n = 30), nasal canula (n = 23), HFNC (n = 5), and mechanical ventilation (n = 2) (Table 2). In the control group, patients received oxygen therapy (n = 56), nasal canula (n = 45), HFNC (n = 8), and mechanical ventilation (n = 3). The administration of oxygen therapy was significantly lower in the treatment group than the control group (6.5% vs. 12.1%, P = 0.0044). All these patients admitted to our hospitals and received additional therapy (remdesivir, baricitinib, and/or corticosteroids). No deaths observed in both groups.

Table 1
Underlying conditions in patients with COVID-19 between the treatment group and the control group[a].

Variables	Treatment group	Control group	*P* value
No. of patients	461	461	
Median age (IQR), years	51 (44–57)	51 (44–57)	>0.9999
No. of males/females	226/235	226/235	>0.9999
No. (%) of patients with risk factors			
Age ≥50 years old	280 (60.7)	280 (60.7)	>0.9999
Obesity with body mass index ≥30 kg/m^2	108 (23.4)	113 (24.5)	0.7577
Cardiovascular diseases including hypertension	127 (27.5)	117 (25.4)	0.5017
Chronic lung diseases including asthma	67 (14.5)	55 (11.9)	0.2850
Diabetes mellitus either type 1 or 2	65 (14.1)	84 (18.2)	0.1071
Chronic kidney disease including those on hemodialysis	13 (2.8)	17 (3.7)	0.5784
Chronic liver failure	19 (4.1)	15 (3.3)	0.6007
Immunosuppressed status[b]	21 (4.6)	14 (3.0)	0.3011
Late pregnancy	3 (0.7)	6 (1.3)	0.5057
Hyperlipidemia	36 (7.8)	62 (13.4)	0.0073
Smoking history	175 (38.0)	161 (34.9)	0.3737
No. (%) of patients with COVID-19 mRNA vaccination			
Never	376 (81.6)	397 (86.1)	0.0733
Once	71 (15.4)	55 (11.9)	0.1502
Twice	14 (3.0)	9 (2.0)	0.3989
Laboratory findings, median (IQR)			
White blood cell count,/μL	4600 (3600–5700)	4500 (3500–5500)	0.6523
C-reactive protein, mg/dL	0.99 (0.35–3.14)	1.08 (0.42–3.26)	0.7354
Aspartate aminotransferase, U/L	31 (22–44)	29 (21–40)	0.5839
Alanine aminotransferase, U/L	26 (18–42)	24 (17–39)	0.6103
No. (%) of patients with oxygen saturation level (room air) at the enrollment			
SpO_2 ≥96%	231 (50.1)	249 (54.0)	0.2624
93% < SpO_2 < 96%	230 (49.9)	212 (46.0)	0.2624

[a] Continuous values are presented as medians and interquartile ranges (IQRs) and categorical/binary values as counts and percentages.
[b] Including those on chemotherapy, organ transplants, poorly controlled human immunodeficiency virus infection, sickle cell anemia, thalassemia, long term use of immunosuppressive medication.

Table 2
Clinical outcome in patients with COVID-19 between the treatment group and the control group[a].

Variables	Treatment group	Control group	*P* value
No. of patients	461	461	
No. (%) of patients that required oxygen therapy	30 (6.5)	56 (12.1)	0.0044
Nasal cannula	23	45	
High flow nasal cannula	5	8	
Mechanical ventilation	2	3	
No. (%) of patients who died	0	0	>0.9999

[a] Categorical/binary values as counts and percentages.

Bierle et al. assessed the impact of vaccination and casirivimab-imdevimab treatment on the clinical outcome of COVID-19 during a period of SARS-CoV-2 Delta surge [12]. They demonstrated that the 28-day hospitalization rate was 2.6% of 112 patients who received treatment with casirivimab-imdevimab, compared to 16.6% of 291 eligible high-risk patients who did not receive casirivimab-imdevimab (Odds Ratio: 0.138, 95% confidence interval: 0.0426–0.4477, p = 0.001). Our results are consistent with findings reported by Bierle et al. and demonstrate that the casirivimab-imdevimab was associated with significantly lower rates of hospitalization in patients with COVID-19 Delta variant in Japan.

A new lineage of SARS-CoV-2, the Omicron (B.1.1.529) variant, has spread rapidly around the world and has already become the predominant variant in Japan from January 2022. Omicron variant have been divided into four distinct sub-lineages: BA.1, BA.1.1, BA.2, BA.3, BA.4., and BA.5.. Recent studies reported that casirivimab-imdevimab treatment is not recommended in patients with COVID-19 Omicron variant because the casirivimab-imdevimab lost antiviral activity against Omicron/BA.1 variant [13,14]. In Japan, however, the sub-lineage BA.2 is now becoming dominant. Casirivimab-imdevimab inhibited Omicron/BA.2, but the $FRNT_{50}$, the titer of monoclonal antibodies required for a 50% reduction in the number of infectious foci, value of this combination therapy was higher by a factor of 43.0–143.6 for Omicron/BA.2 than for an ancestral strain and other variants of concern (Alpha, Beta, Gamma, and Delta variants) [15].

In conclusion, our results demonstrate that the casirivimab-imdevimab combination antibody treatment is associated with reduced rates of requiring oxygen therapy among high-risk patients with COVID-19 Delta variant.

Ethical approval and consent to participate

The study protocol was approved by the Ethics Committee at Kansai Medical University and all participating facilities. Informed consent was obtained from all individual participants in the study.

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Author's contributions

All the authors conceived the study, participated in its design and coordination and collected and managed the data, including quality control. NM and YN drafted the manuscript, and all authors contributed substantially to its revision. All the authors read and approved the final manuscript.

Consent for publication

Not applicable.

Availability of data and materials

The data will not be shared with participant confidentiality.

Declaration of competing interest

The authors declare that they have no conflicts of interest.

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