Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Clinical efficacy of casirivimab-imdevimab antibody combination treatment in patients with COVID-19 Delta variant

Naoyuki Miyashita\textsuperscript{a, b}, Yasushi Nakamori\textsuperscript{b}, Makoto Ogata\textsuperscript{a}, Naoki Fukuda\textsuperscript{a}, Akihisa Yamura\textsuperscript{a}, Yoshihisa Ishiura\textsuperscript{c}

\textsuperscript{a} First Department of Internal Medicine, Division of Respiratory Medicine, Infectious Disease and Allergology, Kansai Medical University, Japan
\textsuperscript{b} Department of Emergency Medicine, Kansai Medical University Medical Center, Japan
\textsuperscript{c} First Department of Internal Medicine, Division of Respiratory Medicine, Oncology and Allergology, Kansai Medical University Medical Center, Japan

\textbf{ARTICLE INFO}

\textbf{Keywords:}
Casirivimab-imdevimab treatment
Monoclonal antibody
COVID-19
Delta variant
SARS-CoV-2

\textbf{ABSTRACT}

\textbf{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.

\textbf{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 fulfilled the inclusion criteria but did not receive casirivimab-imdevimab. The outcome was the requirement of oxygen therapy.

\textbf{Results:} In the treatment group, patients received oxygen therapy (n = 30), nasal cannula (n = 23), high flow nasal cannula (n = 5), and mechanical ventilation (n = 2). In the control group, patients received oxygen therapy (n = 56), nasal cannula (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.

\textbf{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 \cite{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 \cite{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 \cite{6–9}. Subcutaneous casirivimab-imdevimab prevented symptomatic COVID-19 and asymptomatic SARS-CoV-2 infection in previously uninfected household contacts of infected persons \cite{10}, and reduced the incidence of symptomatic COVID-19 over 28 days in infected household contacts \cite{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.
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 Kuruha Hospital, and Kansai Medical University Tenmabashi 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. Applicants with casirivimab-imdevimab are introduced and consulted to our hospitals from Follow-up Center in Osaka prefecture. The 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/m² (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 cannula, 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 cannula (n = 23), HFNC (n = 5), and mechanical ventilation (n = 2) (Table 2). In the control group, patients received oxygen therapy (n = 56), nasal cannula (n = 45), HFNC (n = 8), and mechanical ventilation (n = 3). The administration of oxygen therapy was significantly lower in the control 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

| Variables | Treatment group | Control group | P value |
|-----------|----------------|---------------|---------|
| No. of patients | 461 | 461 |        |
| Median age (QQR), years | 51 (44.57-57) | 51 (44.57-57) | >0.9999 |
| No. of males/females | 226/235 | 226/235 | >0.9999 |
| No. (%) of patients with risk factors | >0.5 | >0.5 | >0.5 |
| Age ≥50 years old | 280 (60.7) | 280 (60.7) | >0.9999 |
| Obesity with body mass index ≥30 kg/m² | 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 | 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 |

* Continuous values are presented as medians and interquartile ranges (IQRs) and categorical/binary values as counts and percentages.

Table 2

| 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 |

* Categorical/binary values as counts and percentages.
Bierle et al. assessed the impact of vaccination and casirivimab-imdevimab combination 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 did not receive casirivimab-imdevimab treatment, compared to 16.6% of 291 eligible high-risk patients who did not receive casirivimab-imdevimab treatment (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 FRNT50, 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.

Funding

No funding was received.

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.

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, 2019. N Engl J Med 2020;382:727–33.
[2] Wagner C, Griesel M, Mikołajewska A, Mueller A, Nothacker M, Kley K, et al. Systemic corticosteroids for the treatment of COVID-19. Cochrane Database Syst Rev 2021;8:CD014963.
[3] Marconi VC, Ramanan AV, de Bono S, Kartman CE, Krishnan V, Liao R, et al. Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial. Lancet Respir Med 2021;9:1407–18.
[4] Ghosh L, Chaimani A, Evrengolu T, Davidson M, Graa C, Schmucker C, et al. Interleukin-6 blocking agents for treating COVID-19: a living systematic review. Cochrane Database Syst Rev 2021;3:CD013881.
[5] Siemieniuk RA, Bartoszko JJ, Ge L, Zeraaakar D, Izovich A, Kum E, et al. Drug treatments for covid-19: living systematic review and network meta-analysis. BMJ 2020;370:m2980.
[6] Baum A, Fulton BO, Wloga E, Copin R, Pascal KE, Russo V, et al. Antibody cocktail to SARS-CoV-2 spike protein prevents rapid mutational escape seen with individual antibodies. Science 2020;369. 1014–8.
[7] Hansen J, Baum A, Pascal KE, Russo V, Giordano S, Wloga E, et al. Studies in humanized mice and convalescent humans yield a SARS-CoV-2 antibody cocktail. Science 2020;369. 1010–4.
[8] Weinreich DM, Sivapalasingam S, Norton T, Ali S, Gao H, Bhere R, et al. REGN- COV2, a neutralizing antibody cocktail, in outpatients with Covid-19. N Engl J Med 2021;384:238–51.
[9] Weinreich DM, Sivapalasingam S, Norton T, Ali S, Gao H, Bhere R, et al. REGN- COV antibody combination and outcomes in outpatients with Covid-19. N Engl J Med 2021;385:e81.
[10] O’Brien MP, Forleo-Neto E, Musser BJ, Isa F, Chan KC, Sarkar N, et al. Subcutaneous REGN-CONV antibody combination to prevent Covid-19. N Engl J Med 2021;385:1184–95.
[11] O’Brien MP, Forleo-Neto E, Sarkar N, Isa F, Hou P, Chan KC, et al. Effect of subcutaneous casirivimab and imdevimab antibody combination vs placebo on development of symptomatic COVID-19 in early asymptomatic SARS-CoV-2 infection. A Randomized Clinical Trial. JAMA 2022;327:432–41.
[12] Bierle DM, Ganesh R, Razonable RR. Breakthrough COVID-19 and casirivimab-imdevimab treatment during a SARS-CoV-2 B1.617.2 (Delta) surge. J Clin Virol 2021;145:105026.
[13] Planas D, Saunders N, Maes P, Guivel-Benhassine F, Planchais C, Buchrieser J, et al. Considerable escape of SARS-CoV-2 Omicron to antibody neutralization. Nature 2022;602:671–5.
[14] Takahata E, Kinosita N, Yamayoshi S, Sakai-Tagawa Y, Fujisaki S, Ito M, et al. Efficacy of antibodies and antiviral drugs against covid-19 Omicron variant. N Engl J Med 2022;386:995–3.
[15] Takahata E, Kinosita N, Yamayoshi S, Sakai-Tagawa Y, Fujisaki S, Ito M, et al. Efficacy of antiviral agents against the SARS-CoV-2 Omicron subvariant BA.2. N Engl J Med Mar 9;NEJMc2201933. doi: 10.1056/NEJMec2201933.