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Original Article

Duration of infectious viral shedding in patients with mild to moderate COVID-19 treated with REGN-CoV2☆

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ABSTRACT

Introduction: New treatment methods, such as REGN-CoV2, have been approved for patients with coronavirus disease (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). However, the effect of the drug on the duration of infectious viral shedding and viral mutations is unknown. In this study, we investigated the clinical efficacy of REGN-CoV2 treatment in patients with mild to moderate disease and compared its antiviral effects against different strains of SARS-CoV-2.

Methods: Viral culture and PCR testing were performed on the pharyngeal swabs collected from 28 patients with COVID-19 who were admitted and treated at Hiroshima University Hospital during the study period. Of these, 23 patients were treated with REGN-CoV2. The patients were classified into the REGN-CoV2(+) and REGN-CoV2(−) groups, and the clinical course was compared between the groups. The 50% inhibitory concentrations (IC_{50}) of REGN-CoV2 against the isolated virus strains were determined.

Results: After treatment with REGN-CoV2, the virus culture positivity rate was greatly reduced. The time to negative viral culture was significantly shorter in the REGN-CoV2(+) group than in the REGN-CoV2(−) group. *In vitro* evaluation of REGN-CoV2 against isolated virus strains also showed efficacy.

Conclusions: REGN-CoV2 treatment was effective in patients with mild COVID-19 and could shorten the period of infectious viral shedding. This may be an important factor in preventing the spread of infection. It may be possible to revise the isolation period for patients with mild disease treated with REGN-CoV2.

1. Introduction

The coronavirus disease (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is progressing. Eighty one percent of the patients suffer from mild to moderate forms of the disease, but 5% of the patients develop critical conditions, such as respiratory failure and shock [1]. One of the reasons for the prolonged epidemic is the emergence of mutated strains, such as the delta variant. Delta strains of SARS-CoV-2 are more infectious and are more likely to cause severe disease than that caused by conventional strains [2]. However, positive factors, such as widespread vaccination and enhanced therapeutic strategies, are also emerging.

The U.S. Food and Drug Administration has approved emergency use authorization for the casirivimab and imdevimab antibody cocktail (REGN-CoV2). REGN-CoV2 is authorized to treat patients with mild to moderate COVID-19 and those at a high risk of progressing to severe COVID-19, but is not authorized for use in patients requiring oxygen therapy [3]. No deaths or cases requiring hospitalization have been reported in 42 patients with COVID-19, aged 65 years or older, treated with REGN-CoV2 [4]. Quantitative polymerase chain reaction (PCR) has confirmed a decrease in viral load on treating patients with REGN-CoV2 [5]. Prophylactic effects have also been reported [6].

☆ All authors meet the ICMJE authorship criteria.

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In Japan, the drug was approved as a special exception in July 2021 and since then, has been administered for the treatment of mild to moderate COVID-19. However, the effect of the drug on the duration of infectious viral shedding is not known, although a decrease in viral load has been reported, based on PCR analysis. Furthermore, it has been reported that viral mutations may reduce the efficacy of antibody-based therapies such as REGN-CoV2 [7,8].

In this study, we investigated the clinical efficacy of REGN-CoV2 treatment in patients with mild to moderate COVID-19 and the detection of SARS-CoV-2 by viral culture, to evaluate the duration of infectious viral shedding at Hiroshima University Hospital. Furthermore, we compared the antiviral effects of REGN-CoV2 against different strains of SARS-CoV-2 isolated from patients.

2. Methods

2.1. Samples and patients

Among patients with COVID-19 admitted to the Hiroshima University Hospital from August 1, 2021, to October 13, 2021, 28 patients with an indication for REGN-CoV2 treatment, who did not require oxygenation and had a risk factor for severe disease, were included. A total of 56 nasopharyngeal swab specimens were collected in 1 mL physiological saline. The first specimen was collected within 1–2 days of hospitalization at the Hiroshima University Hospital. When the viral culture test result was positive and circumstances allowed for follow-up, the duration of infectious virus shedding was investigated by collecting specimens until negative viral culture conversion was observed.

Twenty-three patients were treated with REGN-CoV2 [REGN-CoV2 (+) group], and five patients preferred not to be treated with the antibody cocktail [REGN-CoV2(−) group]. From medical records, we investigated the background and clinical course of all the study participants, including age, sex, and underlying diseases. Clinical history included those reported as risk factors of severe disease [9]. Fever was defined as having a body temperature of 37.5 °C or higher, and patients after organ transplantation or those receiving steroids or biological agents for underlying diseases were considered to be on immunosuppressive therapy. The SARS-CoV-2 vaccines used in this study were Comirnaty (Pfizer-BioNTech) and Moderna COVID-19 Vaccine (Moderna), and participants with two doses of either vaccine were considered as vaccine completers in the study.

2.2. Cell and viral culture

Vero cells expressing TMPRSS2 (VeroE6/TMPRSS2 cells, JCRB1819; JCRB Cell Bank, Japan) were used to culture SARS-CoV-2. The viral culture method used was similar to that described previously [10]. The cells were observed for 5 days to check for cytopathic effects (CPEs), and the infection titer was determined using the $TCID_{50}$ method.

2.3. Quantitative reverse transcription PCR (RT-qPCR)

RT-qPCR was performed as described previously [10]. Nucleic acid extraction of SARS-CoV-2 was performed using the Maxwell® Viral Total Nucleic Acid Purification Kit (Promega Corporation, Madison, WI, USA), and RT-qPCR was performed using the One Step PrimeScript™ III RT-qPCR mix (Takara Bio Inc., Japan). The N gene was targeted with a forward primer (2.4 μM), 5′-AAA TTT TGG GGA CCA GGA AC-3′; reverse primer (3.2 μM), 5′-TGG CAG CTG TGT AGG TCA AC-3′; and probe (0.4 μM) 5′-FAM-ATG TCG CGC ATT GGC ATG GA-BHQ-3′. The method was performed according to the manufacturer's protocol.

2.4. Mutant strain test

To detect N501Y mutation in the alpha strains and L452R mutation in the delta strains, we used Primer/Probe N501Y (SARS-CoV-2) and Primer/Probe L452R (SARS-CoV-2) Ver.2 (Takara Bio Inc., Japan), and the test was performed using the same procedure as RT-qPCR. The method used was in accordance with the manufacturer's instructions.

The 50% inhibitory concentration (IC_{50}) of REGN-CoV2.

The conventional strain (SARS-CoV-2/JP/Hiroshima-46059T/2020, GISAID accession ID: EPI_ISL_6289932, GenBank/DDBJ/EMBL accession number: MZ853926), without the L452R or N501Y mutation was isolated in Hiroshima Prefecture in 2020. This strain was tested, along with a virus strain isolated at the time of initial specimen collection from a randomly selected patient in the REGN-CoV2(+) group in this study. The virus isolated from the treatment group was found to be the L452R mutant strain (SARS-CoV-2/JP/HiroC81c/2021, GISAID accession ID: EPI_ISL-6756504, GenBank/DDBJ/EMBL accession number: OL638163). The IC_{50} of casirivimab and imdevimab, which constitute REGN-CoV2, were then determined.

To 100 μL of the reaction mixture, casirivimab and imdevimab were added at concentrations of 0.008–1.25 μg/mL and virus at 1 $TCID_{50}$/μL. After incubating at 37 °C for 1 h, VeroE6/TMPRSS2 cells were used to culture these samples. The CPEs were observed for 5 days and the IC_{50} value was calculated as described previously [11].

Ethical approval

This study was approved by the Ethical Committee for Epidemiology of Hiroshima University (approval number: E−2157). The requirement for obtaining written informed consent was waived by the ethics review board because only the patients' clinical specimens and anonymized patient information were used in this study; the patients also had the right to opt out of the use of their surplus patient samples and medical data for research.

2.5. Statistical analysis

For the baseline, medians and interquartile ranges (IQRs) were given for continuous variables, and percentages were given for categorical variables. The Wilcoxon rank-sum test was used to compare continuous variables between the two groups, whereas Fisher's exact test was used to compare categorical variables.

Kaplan–Meier analysis was used to compare time from disease onset to negative viral culture and fever resolution, and estimates were compared using the log-rank test. The data were censored on the date of discharge. Age- and sex-adjusted hazard ratios (HRs) for the REGN-CoV2 (+) group compared to the REGN-CoV2(−) group were calculated using the Cox proportional hazards model.

Statistical significance was set at $p < 0.05$. Statistical analysis was performed using STATA version 16.1 (StataCorp LP, College Station, TX, USA).

3. Results

3.1. Patient background and clinical course

Twenty-three patients were treated with REGN-CoV2, and five patients were not treated with REGN-CoV2. REGN-CoV2 was administered from day 0 to day 8 after symptom onset, with a median of 4 days. Table 1 shows the patient's background and clinical course. The median patient age was 59.5 years [REGN-CoV2(+) group: 57.0 years, REGN-CoV2(−) group: 68.0 years; $p = 0.74$]. Of the total patients, 60.7% were male [REGN-CoV2(+) group: 60.9%, REGN-CoV2(−): 42.9%; $p = 0.62$].

The number of patients with a history of cardiovascular disease was significantly higher in the REGN-CoV2(+) group ($p = 0.041$) than in the REGN-CoV2(−) group. There was no difference in the number of vaccinations between the two groups ($p = 0.80$), and there were significantly more L452R mutant strains in the REGN-CoV2(+) group ($p = 0.18$).

Fever was observed in 85.7% of the patients, and there was no

Table 1
Patient characteristics and clinical course.

Characteristics	REGN CoV2 (+) group	REGN CoV2 (−) group	p-value
Number of patients	**23**	**5**	
Median age (range, IQR) -years	57.0 (48–76)	68.0 (61–72)	0.74
Male sex - no. (%)	14 (60.9)	3 (42.9)	0.62
Median BMI (range, IQR) -kg/m^2	25.2 (21.9–29.4)	21.9 (21.2–22.8)	0.11
Risk Factor for COVID-19			
Age ≧50 years -no. (%)	17 (73.9)	4 (80.0)	1
Cardiovascular disease -no. (%)	14(60.9)	0(0.0)	0.041
BMI ≧25 -no. (%)	12(52.2)	1(20.0)	0.33
Immunosuppression therapy -no. (%)	3(13.0)	1(20.0)	1
Chronic kidney disease -no. (%)	4(17.4)	0(0.0)	1
Diabetes mellitus -no. (%)	5(21.7)	0(0.0)	0.55
Pregnancy -no. (%)	2(8.7)	0(0.0)	1
Number of doses of SARS-CoV-2 Vaccinations			0.80
0 - no. (%)	12(52.2)	4(80.0)	
1 - no. (%)	6(26.1)	0(0.0)	
2 - no. (%)	5(21.7)	1(20.0)	
Laboratory test			
Median Creatine Kinase (range, IQR) -IU/L	89 (66–161)	69 (48–76)	0.39
Median Lactate dehydrogenase (range, IQR) U/L	207 (187–250)	266 (261–278)	0.69
Median C–reactive protein (Median, IQR) -mg/dL	1.37 (0.07–1.98)	1.09 (0.16–2.18)	0.61
Median White blood cells 10^3 (range, IQR) -/μL	6.55 (5.16–8.37)	5.13 (4.92–5.16)	0.063
Median Lymph 10^3 (range, IQR) -/μL	1.35 (0.98–1.91)	1.38 (0.94–1.52)	0.42
Virus strain			0.18
N501Y(+), L452R(−) -no. (%)	0(0.0)	1(20.0)	
L452R(+), N501Y(−) -no. (%)	23(100.0)	4(80.0)	
Clinical courses			
Fever -no. (%)	21(91.3)	3(60.0)	0.14
Median duration of fever (range, IQR) -days	3.0(2–6)	6.0(0–8)	0.14
Confirmation of Culture Negative -no. (%)	19(82.6)	4(80.0)	1
Oxygen therapy during hospitalization -no. (%)	8(34.8)	2(40.0)	1
Median duration of oxygen therapy (range, IQR) -days	2.5(1.5–3.5)	6(6–6)	0.52
Steroid therapy during hospitalization -no. (%)	2(8.7)	2(40.0)	0.14
Remdesivir treatment during hospitalization -no. (%)	3(13.0)	2(40.0)	0.21
Median duration from onset to Culture Negative (range, IQR) -days	7.0(3–11)	10.0(9–14)	0.0041

IQR, interquartile range; BMI, body mass index.

significant difference in the duration of fever (p = 0.14). Of the total patients, 14.3% assented to steroid therapy during hospitalization [REGN-CoV2(+) group: 8.7%, REGN-CoV2(−): 40%; p = 0.14], and 17.9% assented to remdesivir therapy during hospitalization [REGN-CoV2(+) group: 13.0%, REGN-CoV2(−): 40%; p = 0.21]. Of all the patients, 82.1% were confirmed as culture negative [REGN-CoV2(+) group: 82.6%, REGN-CoV2(−): 80%; p = 1]. The median number of days after the onset of illness, when negative cultures were confirmed, for the REGN-CoV2(+) group (7.0 days) was significantly lesser than that for the REGN-CoV2(−) group (10.0 days; p = 0.0041).

3.2. Change in viral load among patients treated with REGN-CoV2

The first specimen was collected at a median of 3 days after hospitalization [REGN-CoV2(+) group: 3 days, REGN-CoV2(−): 4 days; p = 0.14]. Viral culture and PCR tests were performed on 42 samples collected from 23 patients treated with REGN-CoV2 (Fig. 1). The viral load of the first sample, determined by viral culture, was 7.4×10^5 $TCID_{50}$/mL [REGN-CoV2(+) group: 1.1×10^6 $TCID_{50}$/mL, REGN-CoV2(−): 2.0×10^5 $TCID_{50}$/mL; p = 0.70] and 5.0×10^7 copies/mL by PCR [REGN-CoV2(+) group: 3.7×10^7 copies/mL, REGN-CoV2(−): 8.0×10^7 copies/mL; p = 0.57]. Results from both the methods revealed that the viral load decreased after REGN-CoV2 administration. Samples were collected at a median of 2 days after REGN-CoV2 administration. Only one of the 19 samples was culture positive after REGN-CoV2 administration.

3.3. Clinical courses of REGN-CoV2(+) group and REGN-CoV2(−) group

The REGN-CoV2(+) group showed an approximately 3.8 times higher tendency to shorten the time from disease onset to negative viral culture than the REGN-CoV2(−) group (age- and gender-adjusted HR 3.78; 95 %CI; 1.04–13.7) (Fig. 2a). However, the time to fever resolution was not significantly shorter in the REGN-CoV2(+) group than in the REGN-CoV2(−) group (age-gender-adjusted HR, 2.08; 95 %CI, 0.58–7.49) (Fig. 2b).

3.4. IC_{50} of casirivimab and imdevimab

IC_{50} of casirivimab and imdevimab against the clinical isolate L452R variant strain and the conventional strain are shown in Fig. 3. The IC_{50} of the conventional strain was 0.16 μg/mL for casirivimab and 0.19 μg/mL for imdevimab (Fig. 3a). In the L452R variant strain, the IC_{50} value was 0.18 μg/mL for casirivimab and 0.68 μg/mL for imdevimab (Fig. 3b).

4. Discussion

The study showed that REGN-CoV2 administration significantly shortened the period of viral culture.

The duration of viral culture positivity in 23 patients with REGN-CoV2 was significantly reduced. A decrease in the rate of positive viral cultures a day after treatment suggests a reduction in the duration of infectious viral shedding.

In the REGN-CoV2(−) group, one patient showed a positive culture on day 11. In this case, oxygen was administered until day 10, steroid treatment was administered until day 12, and the specimen on day 14 was culture-negative. For the case that was culture-positive on day 10 of onset, the specimen on day 11 was negative. Thus, isolation is recommended for mild to moderate cases until 10 days after onset and 24 h after the disappearance of symptoms, such as fever [12]. In the REGN-CoV2(−) group, it was considered necessary to follow this recommendation. In contrast, the REGN-CoV2(+) group showed culture-negativity earlier than the REGN-CoV2(−) group, suggesting that isolation for 10 days after the onset of illness may not be necessary.

Although there was no significant difference in the frequency of oxygenation, fewer patients in the REGN-CoV2(+) group required further treatment with steroids. The median duration of oxygen administration was 3 days in the REGN-CoV2(+) group and 6 days in the REGN-CoV2(−) group (p = 0.52). Although the difference was not significant, even if oxygen is required, symptoms in the REGN-CoV2(+) group may be milder than those in the REGN-CoV2(−) group.

Nine specimens were collected on days 0–2 of oxygen administration; all 5 specimens without REGN-CoV2 treatment were culture positive, with viral loads ranging from 1.1×10^5 to 3.6×10^8 $TCID_{50}$/mL. However, only one of the four specimens from the REGN-CoV2-treated specimens was positive, and the viral load of that specimen was also low, at 3.6×10^2 $TCID_{50}$/mL. Although the number of cases being compared was small, the data strongly suggest that, despite oxygen therapy being initiated in both the groups, the viral load in the REGN-CoV2(+) group during oxygen administration was lower than that in the REGN-CoV2(−) group.

Steroids were administered to four patients, among which, three specimens from day −1 to day 1 of steroid administration were culture

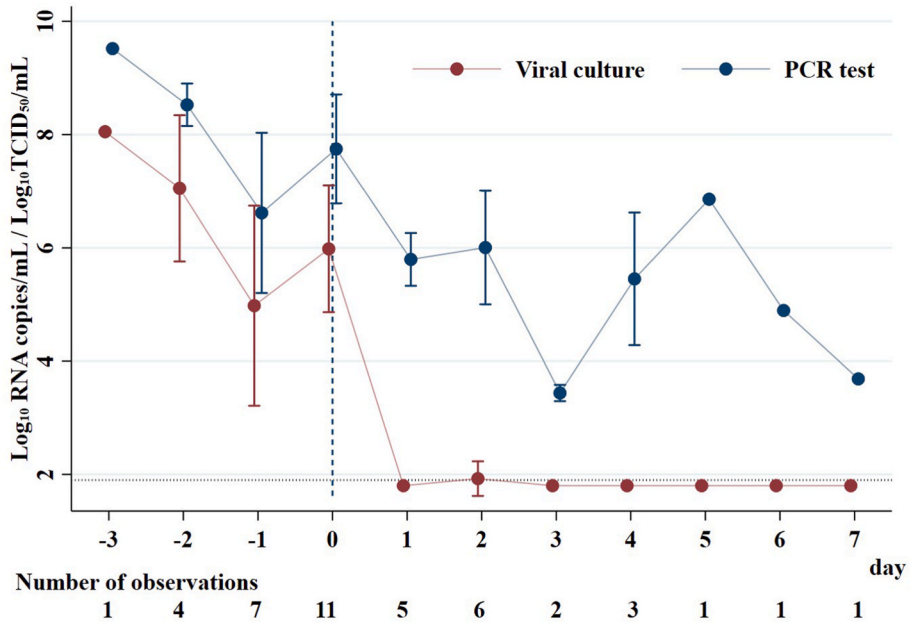

Fig. 1. Viral load of samples of post REGN-CoV2 treatment.
PCR, polymerase chain reactiondays,
the number of days after initiation of treatment with REGN-CoV2.
Line graph with error bars showing the mean viral dose by viral culture and PCR after hospitalization.
Error bars indicate standard deviation.

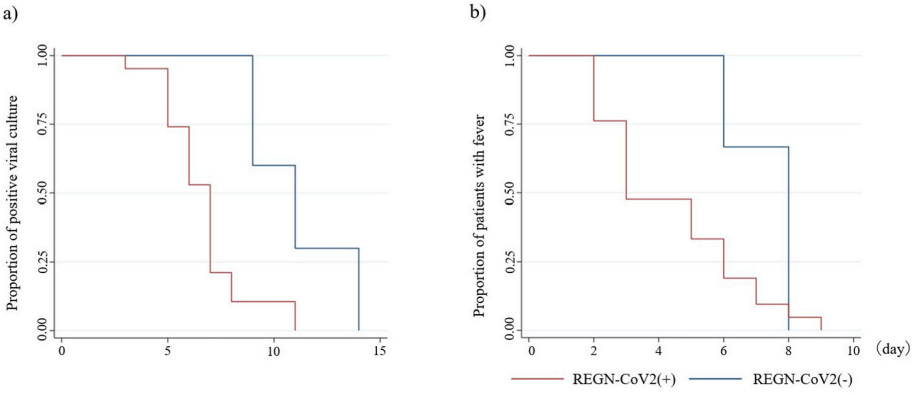

Fig. 2. Duration of time to negative culture and fever resolution
a) The proportion of positive viral culture patients. The time to culture negative was checked to investigate the duration of infectious viral shedding.
b) The proportion of patients with fever. The time to fever resolution was studied.
days, the number of days after onset.

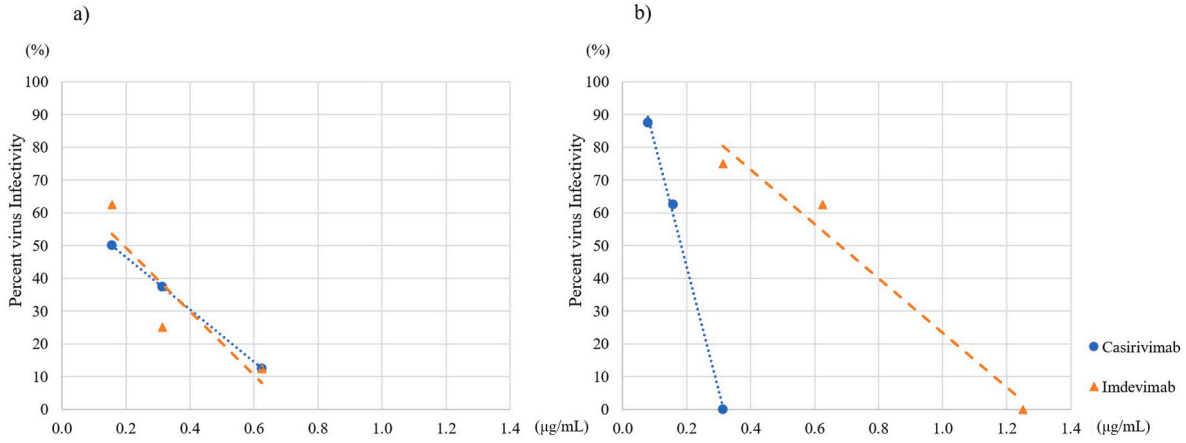

Fig. 3. The 50% inhibitory concentration (IC_{50}) of REGN-CoV2: Percent virus infectivity
a) Conventional strain
b) L452R strain
The values of different concentrations were plotted and exponential approximation was performed in Excel to calculate the concentration of drug required to reduce viral load by 50%.

negative. This suggests that there was very little or no infectious viral shedding on the day of steroid administration. For one patient in the REGN-CoV2(−) group, steroid treatment was started on day 5 after onset, and viral cultures were quantified at 1.1×10^5 $TCID_{50}$/mL on days 4 and 7. On the day 11 after onset, 2.0×10^5 $TCID_{50}$/mL viral load was detected, and negative culture was confirmed on day 14. As this was the only case of steroid administration to a patient with infectious viral shedding, it is difficult to draw conclusions; however, it is possible that the duration of infectious viral shedding may be prolonged.

The IC_{50} for casirivimab was similar to those of the conventional strains isolated in 2020, without L452R or N501Y mutations, but the IC_{50} for imdevimab was higher in strains with the L452R mutation than that in the conventional strains. These findings suggest that imdevimab may be less effective in strains with the L452R mutation.

The blood concentrations of casirivimab and imdevimab decrease over time after administration, and the mean concentrations (±standard deviation) on day 29 after administration have been reported to be 68.0 ± 45.2 mg/L and 64.9 ± 53.9 mg/L, respectively [5]. Although the IC_{50} was marginally higher for imdevimab against the L452R mutant strain, the blood concentration during treatment was considered to be above the IC_{50}, and both casirivimab and imdevimab may have been clinically effective. In practice, cases of the L452R mutant strain treated with REGN-CoV2 had immediate negative viral cultures. Although no effective cutoff value for IC_{50} has been established, we considered it to be effective in this study.

This study had several limitations. This was a retrospective single-center study with a small sample size. There was a difference in the number of patients in both the groups because we did not randomly select patients to receive REGN-CoV2, but rather decided whether to administer it based on patient preference.

Patients with risk factors for severe disease were more likely to be in the REGN-CoV2(+) group, but such patients were more likely to request REGN-CoV2 even if they had the same severity of disease. The number of patients receiving two doses of the COVID-19 vaccine were similar, but the number who had not received any vaccine tended to be lower in the REGN-CoV2(+) group than in the REGN-CoV2(−) group. This may be because there has been a strong preference to vaccinate patients with risk factors for severe diseases. Ten patients required oxygen therapy during the course of their hospitalization. Four patients were treated with steroids, and five patients were treated with remdesivir.

In addition, since sample retrieval was not possible every day, the time to culture negative may have been overestimated. The IC_{50} of casirivimab and imdevimab could not be evaluated using only a small number of strains.

Although the peak viral load was similar between fully vaccinated and unvaccinated patients, the mean decrease in viral load was faster in vaccinated patients than in unvaccinated patients (posterior probability >0.84) [13]. In the present study, the median viral load by culture at the time of initial specimen collection was 5.8×10^5 $TCID_{50}$/mL in vaccine completers and 7.4×10^5 $TCID_{50}$/mL in vaccine non-completers ($p = 0.43$). Five patients in the REGN-CoV2(+) group completed vaccination, and two patients (40%) required oxygen during the course of hospitalization. Only one patient in the REGN-CoV2(−) group completed vaccination, viral culture remained positive until day 7 of disease onset, and negative culture was confirmed on day 9. Because of the small number of cases, we were unable to identify the factors that led to negative culture in the vaccine completers.

Vaccination, severity factors, and treatment may affect the duration of infectious viral shedding, but in this study, the difference between the two groups was not excluded because REGN-CoV2 was administered according to patient preference.

The incidence of COVID-19-related hospitalization or all-cause mortality has been reported to be 1.0% in the REGN-CoV2 group vs. 3.2% in the placebo group ($p = 0.002$), indicating an improvement with REGN-CoV2 [14]. None of the 28 cases included in this study developed severe disease or death, and no significant differences in clinical course were observed.

However, in the REGN-CoV2(−) group, the isolation period recommended for patients with mild to moderate disease was considered necessary, but in the REGN-CoV2(+) group, the positivity rate of the viral culture after the day following treatment was markedly reduced, and the time to culture-negativity was shortened.

5. Conclusion

We evaluated the efficacy of REGN-CoV2 using different methods, including changes in viral load, clinical course, and *in vitro* antiviral effects. In particular, the time to negative viral culture was significantly shortened, suggesting that the period of infectious viral shedding was shortened. A rapid decrease in viral load and negative cultures may be an important factor in preventing the spread of infection. With the accumulation of further data, it may be possible to revise the isolation period for patients with mild disease treated with REGN-CoV2.

Author Contribution

This study was designed and supervised by MI, TS, and HO. T. Nomura, HK, KO, YK, and NS collected samples and clinical data, which were analyzed by T. Nomura, MK, TN, and DM. All authors contributed to the interpretation of data. The final manuscript was reviewed by all authors.

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Declaration of interest

None.

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None.

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