Original Article

REGN-COV2 antibody cocktail in patients with SARS-CoV-2: Observational study from a single institution in Japan

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ABSTRACT

Introduction: A new treatment for coronavirus disease (COVID-19), REGN-COV2, a cocktail consisting of two neutralizing antibodies against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been approved for patients at a risk of developing more severe disease.
Methods: We retrospectively reviewed patients recently diagnosed with COVID-19 with risk factors for severe infection, who were treated with the REGN-COV2 antibody cocktail between July and September 2021. The REGN-COV2 antibody cocktail was administered to patients within 7 days of disease onset, with an oxygen saturation of >93%, and with at least one comorbidity. We investigated the percentage of patients with COVID-19-related hospitalization or death, the duration of symptoms after treatment, and the adverse effects of treatment.
Results: A total of 108 patients were reviewed. Of them, 64% were aged ≥50 years, 31% had obesity, 36% had hypertension, and 18% had diabetes. In addition, 49% had multiple risk factors for severe COVID-19. Overall, 12 patients (11%) needed COVID-19-related hospitalization. No adverse effects of treatment were observed.
Conclusions: This study shows that treatment with the REGN-COV2 antibody cocktail is safe and beneficial in patients at a risk of developing severe COVID-19.

1. Introduction

Coronavirus disease (COVID-19) has emerged as a global pandemic since the first identification of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in December 2019. With the aim of ending the COVID-19 pandemic, effective vaccines have been developed and vaccinations are progressing; however, the pandemic is far from over and Japan is no exception. The fifth wave of COVID-19 infections, characterized by infections in younger individuals, hit Japan in August 2021.

Although many patients with COVID-19 have mild or moderate disease, 15% experience severe disease and 5% progress to critical illness [1]. It has been reported that individuals with certain underlying conditions, such as older age [2], cardiovascular disease [3], chronic lung disease [4], chronic kidney disease [5], diabetes [6], obesity [7], or immunocompromised status [8], are at a high risk of adverse COVID-19 outcomes. Several risk factors have been identified as indicators of the progression of COVID-19. Elevations of C-reactive protein (CRP) or

lactase dehydrogenase (LDH) levels are reported to be associated with severe disease, and interferon lambda 3 (IFN-λ3) is also reported to increase in elevation a couple days before the progression of disease. These are used to predict the course of the disease in clinical practice [9–12]. The treatment of COVID-19 has also progressed, with the systemic steroid dexamethasone [13], the antiviral agent remdesivir [14–16], and the Janus kinase inhibitor baricitinib [17] being currently available for patients with severe disease in Japan. Recently, REGN-COV2, an antibody cocktail, has been approved for patients with mild to moderate disease who are at a risk of developing more severe symptoms. REGN-COV2 contains two SARS-CoV-2-neutralizing antibodies, casirivimab and imdevimab, which bind the spike protein of SARS-CoV-2 to prevent viral entry into human host cells [18]. In a previous phase III clinical trial, the REGN-COV2 antibody cocktail was shown to reduce the number of patients with a COVID-19-related hospitalization or death by approximately 70% compared to the placebo group. To prevent the collapse of the medical care system, it is important to decrease the number of hospitalized patients requiring a high level of medical care.

Abbreviations

BMI   body mass index
COVID-19   coronavirus disease
CRP   C-reactive protein
IFN-λ3   interferon lambda 3
LDH   lactase dehydrogenase
RT-PCR   reverse transcription polymerase chain reaction
SARS-CoV-2 severe acute respiratory syndrome coronavirus 2
SpO$_2$ oxygen saturation

Therefore, the REGN-COV2 antibody cocktail offers hope for ending the current pandemic; however, little is known about the actual efficacy and adverse effects in clinical practice. In this study, we investigated the characteristics of patients who received the REGN-COV2 antibody cocktail, as well as the efficacy and adverse effects of this treatment, at our institution.

2. Materials and methods

2.1. Patients and study design

We retrospectively reviewed patients who were diagnosed with COVID-19 and received the REGN-COV2 antibody cocktail at Tokyo Women's Medical University Medical Center East between July and September 2021. All patients were confirmed to have SARS-CoV-2 infection through real-time reverse transcription polymerase chain reaction (RT-PCR) or antigen testing. At the physician's discretion, the REGN-COV2 antibody cocktail was used in patients within 7 days of disease onset, with an oxygen saturation (SpO$_2$) of >93% (room air), and with at least more than one of the following conditions: age ≥50 years, body mass index (BMI) ≥30 kg/m^2, cardiovascular disease (including hypertension), chronic lung disease (including asthma), type 1 or type 2 diabetes, chronic kidney disease (including dialysis requirement), chronic liver disease, or an immunocompromised status. In Japan, all SARS-CoV-2-positive cases are reported to the relevant jurisdictional public health-care center. The health-care center collects information from each patient, including background characteristics, underlying conditions, and current conditions; selects patients who need hospitalization; and sends requests for admission to each medical center. At the time of the approval of the REGN-COV2 antibody cocktail in Japan, the treatment was allowed to be used only in hospitalized patients, who were observed for the occurrence of serious adverse events such as infusion reactions. At admission, the patients underwent vital sign assessments, body measurements, blood test, RT-PCR test with nasopharyngeal swab, and chest radiography. LightMix® Molecular SARS-CoV (COVID-19) (Roche Diagnostics K.K., Tokyo, Japan) was used for the SARS-CoV-2 RT-PCR tests. After admission, we assessed if each candidate met all treatment criteria. Patients who did not meet the criteria, such as those with lower SpO$_2$ (<93%), were excluded from treatment with REGN-COV2.

This study was approved by the institutional review board (IRB) of Tokyo Women's Medical University. (IRB number 2021-0107)

2.2. Treatments and treatment outcomes

The REGN-COV2 antibody cocktail, consisting of 120 mg casirivimab and 120 mg imdevimab, was intravenously administered on the day of admission. Each patient was carefully monitored for adverse events during and after the administration of REGN-COV2. Adverse events include any unfavourable events that occurred both during and after the administration of REGN-COV2. Patients had their condition monitored by the health-care center up to 10 days after the onset and 72 h after the resolution of fever in pyretic patients. A pulse oximeter was distributed to the patients for home use, and the health-care center regularly assessed the patients' condition, including symptoms and SpO$_2$ levels. If patients were suspected to progress in severity, by attending physician at admission, the attending physician extended the patient in hospital stay and were under observation after the cocktail treatment. When the patients progressed to a severe or a critical state, they were aggregated as part of COVID-related hospitalization. Patients who required re-hospitalization due to progression of the severity of the disease during observation by the health-care center were also aggregated as COVID-19-related hospitalization. The treatment outcomes included the need for COVID-19-related hospitalization or COVID-19-related death. We collected information about each patient's condition after the administration of REGN-COV2 from the health-care center.

2.3. Statistical analysis

The study population included all patients who received the REGN-COV2 antibody cocktail since the approval of the drug in July 2021 and who had available follow-up data on clinical course and outcome from the health-care center. Abnormal data related to COVID-19 hospitalization was defined by exceeding the upper limit of normal data in our institution. We conducted an experimental analysis to determine the factors associated with COVID-19-related hospitalization. Sex, age, BMI, comorbidities (obesity, cardiovascular disease, diabetes), meeting more than two criteria for REGN-COV2, history of vaccinations, body temperature and SpO2 at the time of treatment, symptom duration before admission, viral load (Ct value), CRP level, LDH level, IFN-λ3 level, and presence of pneumonia on radiography were evaluated as risk factors. The associations between treatment outcomes and patient characteristics were evaluated using the chi-square test, *t*-test, or the Mann-Whitney *U* test. We conducted the Shapiro-Wilk test to identify whether or not the data was normally distributed. A *t*-test was used for normally distributed continuous variables, and the Mann-Whitney *U* test was used for non-normally distributed variables. Statistical analyses were performed using R (version 3.3.3, March 6, 2017).

3. Results

3.1. Patient characteristics

A total of 108 patients received the REGN-COV2 antibody cocktail. The characteristics of the enrolled patients are summarized in Table 1. The median age was 52 years, and 64% of the patients were aged ≥50 years. The median BMI was 26.3 kg/m^2. Overall, 31% patients had obesity (BMI >30 kg/m^2), 36% had cardiovascular disease. Patients with cardiovascular disease, all had hypertension. Most patients with chronic lung disease had asthma. Patients with chronic kidney disease included 2 patients undergoing hemodialysis treatment. Among the patients, 49% met more than two criteria for treatment with the REGN-COV2 antibody cocktail. Information about vaccination was missing in four patients. Of the remaining patients, 12% had received one vaccination dose of either the Pfizer Inc. or Moderna, Inc. vaccine and 26% had completed two COVID-19 vaccination doses. At the time of admission, 27% had fever (≥37.5 °C). Among all patients, 11% had an SpO$_2$ of between 93% and 95% (room air). The median duration of symptoms before the administration of REGN-COV2 was 4 days, and 48% of the patients received the treatment after 5 days of onset. Data of RT-PCR tests with nasopharyngeal swabs at admission were available in 81% of all patients. Except for one patient, all patients were infected with the delta variant of SARS-CoV-2. The median threshold cycle (Ct) of target genes E and N was 20.9 and 26.7, respectively. The median levels of C-reactive protein (CRP), lactate dehydrogenase (LDH), and IFN-λ3 were 1.05 mg/dL, 238 IU/L, and 5.8 pg/mL, respectively. Pneumonia was detected on chest radiography in 69% of the patients at admission.

Table 1
Baseline characteristics.

	n = 108
Male sex (%)	68 (63)
Age (years)	Median 52 (range: 24–89)
Age >50 years (%)	69 (64)
BMI	Median 26.3 (range: 16.4–39.7)
Comorbidities	
BMI >30 kg/m^2 (%)	34 (31)
Cardiovascular disease (%)	39 (36)
Chronic lung disease (%)	14 (13)
Diabetes (%)	19 (18)
Chronic kidney disease (%)	3 (3)
Chronic liver disease (%)	3 (3)
Immunocompromised status	
Cancer patients (%)	3 (3)
Patients on immunosuppressants (%)	3 (3)
More than two criteria for REGN-COV2 (%)	53 (49)
Vaccinations[a]	
None (%)	65 (63)
One dose (%)	12 (12)
Two doses (%)	27 (26)
Body temperature (°C)	Median 37.0 (range: 35.5–39.0)
SpO$_2$ (%, room air)	Median 97 (range: 93–99)
SpO$_2$ 93–95% (room air) (%)	12 (11)
Symptom duration before admission (days)	4 (range: 1–7)
Symptom duration before admission ≥5 days	52 (48)
Median viral load (Ct[b] value)	
Target gene E	Median 20.9 (range: 12.2–34.5)
Target gene N	Median 26.7 (range: 18.0–35.0)
Baseline serum CRP level (mg/dL)	Median 1.05 (range: 0.05–23.0)
Baseline serum LDH level (U/L)	Median 238 (range: 149–807)
Baseline serum IFN-λ3 level (pg/mL)	Median 5.8 (range: <3–71.3)
Pneumonia on radiography (%)	75 (69)

BMI, body mass index; SpO$_2$, oxygen saturation; CRP, C-reactive protein; LDH, lactase dehydrogenase; IFN-λ3, interferon lambda 3.
[a] Data were missing in four patients.
[b] Ct denotes the cycle threshold of the RT-PCR assay.

3.2. Treatment outcomes

All patients were followed up by the health-care center until recovery from symptoms or COVID-19-related hospitalization. No adverse events, such as infusion reaction due to treatment with the REGN-COV2 cocktail antibody, were observed. After the treatment, the number of patients with COVID-19-related hospitalization, due to decreased SpO$_2$, was 12, accounting for 11% of the enrolled patients who received REGN-COV2. There were no cases in which patients who needed COVID-19-related hospitalization were rejected because of a lack of COVID-19 bed capacity. No deaths were reported. Patients with COVID-19-related hospitalization due to exacerbation of pneumonia were treated with steroids with or without remdesivir; however, one patient required intubation. None of the patients who had completed vaccination needed COVID-19-related hospitalization after the treatment.

We conducted an experimental analysis to determine the factors associated with the need for COVID-19-related hospitalization owing to COVID-19 exacerbation (Table 2). Univariate analysis showed that low SpO$_2$ at the time of treatment (p = 0.004), CRP level (p < 0.001), LDH level (p < 0.001), IFN-λ3 level (p < 0.001), and presence of pneumonia on radiography (p = 0.039) were significantly associated with the need for COVID-19-related hospitalization. Moreover, we categorized patients into two risk groups according to the number of abnormal data (CRP level >0.3 mg/dL, LDH level >222 U/L, and IFN-λ3 level >13.6 pg/mL). Patients with 0–1 and 2–3 abnormal data were categorized into the no-risk group and at-risk group, respectively. There were 49 patients in the no-risk group, and 59 patients in the at-risk group. Twelve patients in the at-risk group required hospitalization due to exacerbations. The rate of COVID-19-related hospitalization was 0% in the no-risk group and 20% in the at-risk group. The comparison of background characteristics in at-risk patients (2–3 abnormal data) with and without

Table 2
Comparison between patients with and without the need for COVID-19-related hospitalization.

	No hospitalization (n = 96)	Hospitalization (n = 12)	p Value
Male sex (%)	57 (59)	11 (92)	0.062[a]
Age (years)	Median 52 (range: 24–89)	Median 56 (range: 45–86)	0.12[c]
Age >50 years (%)	59 (61)	10 (83)	0.24[a]
BMI	Median 26.2 (range: 16.4–39.7)	Median 27.7 (range: 17.3–37.4)	0.63[b]
BMI >30 kg/m^2 (%)	30 (31)	4 (33)	1[a]
Cardiovascular disease (%)	35 (36)	4 (33)	1[a]
Chronic lung disease (%)	13 (14)	1 (8)	0.96[a]
Diabetes (%)	15 (16)	4 (33)	0.26[a]
More than two criteria (%)	46 (48)	7 (58)	0.71[a]
Vaccination completed (%)	27 (28)	0	0.067[a]
Body temperature (°C)	Median 37.0 (range: 35.5–39.0)	Median 37.1 (range: 36.2–38.8)	0.38[b]
SpO$_2$ 93–95% (room air) (%)	7 (7)	5 (42)	0.004[a]
Symptom duration (days)	Median 4 (range: 1–7)	Median 6 (range: 2–7)	0.17[c]
Median viral load (Ct** value)			
Target gene E	Median 21.1 (range: 12.2–34.5)	Median 20.4 (range: 14.9–28.9)	0.98[c]
Target gene N	Median 27.0 (range: 18.0–35.0)	Median 27.9 (range: 20.9–33.8)	0.91[c]
CRP level (mg/dL)	Median 0.86 (range: 0.05–17.3)	Median 7.6 (range: 3.4–23.0)	<0.001[c]
LDH level (IU/L)	Median 227 (range: 149–807)	Median 356 (range: 240–743)	<0.001[c]
IFN-λ3 level (pg/mL)	Median 4.8 (range: < 0.3–38.3)	Median 15.7 (range: 4.7–71.3)	<0.001[c]
Pneumonia on radiography (%)	63 (66)	12 (100)	0.039[a]

BMI, body mass index; SpO$_2$, oxygen saturation; CRP, C-reactive protein; LDH, lactase dehydrogenase; IFN-λ3, interferon lambda 3.
[a] Chi-square test.
[b] t-test.
[c] Mann-Whitney *U* test.

the need for COVID-19-related hospitalization is shown in Supplementary Table S1. An SpO$_2$ of 93–95% (room air) at admission in at-risk patients was significantly associated with COVID-19-related hospitalization. Between the no-risk group and the at-risk group, median level of CRP and IFN-λ3 also showed a significant difference.

4. Discussion

We investigated the clinical efficacy and safety of the REGN-COV2 antibody cocktail consisting of casirivimab and imdevimab in patients at a high risk of severe and critical COVID-19. The previous phase III clinical trial of the REGN-COV2 antibody cocktail showed a significant reduction in the risk of COVID-19-related hospitalization by 70% compared to placebo. Our study patients had at least one risk factor for severe COVID-19, such as age ≥50 years (51%), obesity (58%), or cardiovascular disease including hypertension (36%) [16]. In Japan, the use of the REGN-COV2 antibody cocktail was limited to patients with at least one of the following conditions: age ≥50 years, BMI ≥30 kg/m^2, cardiovascular disease, chronic lung disease, diabetes, chronic kidney disease, chronic liver disease, or immunocompromised status. In our study, many patients were aged >50 years (64%), had a BMI of >30 kg/m^2 (31%), and had hypertension (36%). Notably, 49% met more than two criteria for REGN-COV2 treatment. The rate of COVID-19-related hospitalization after treatment with the antibody cocktail was 11%. The rate of COVID-19-related hospitalization without

treatment in this study group is unknown. In general, 20% require oxygen support because of progression to severe to critical disease [1]; however, certain conditions increase the risk of severe COVID-19 [9]. For example, it has been reported that approximately 40% of patients aged ≥65 years progress to severe or critical disease, compared to 17% of patients aged between 18 and 64 years [19]. Moreover, a large cohort study showed an increased risk of COVID-19-related hospitalization and increased disease severity, with risk ratios of 2.2 and 2.3, respectively, in patients with obesity [20]. Hypertension has also been reported to increase the risk of severe COVID-19, with a risk ratio of 2.01 [21]. In addition, almost all patients in our study were infected with the delta variant, which started spreading only after the previous phase III clinical trial of the REGN-COV2 antibody cocktail. There are studies indicating that patients with SARS-CoV-2 delta variant have a higher risk of hospital admission compared to the previous variants [22,23].

Taken together, the possible rate of progression to severe or critical disease in our study group in the absence of treatment with the REGN-COV2 antibody cocktail is expected to be high.

Reports on REGN-COV2 antibody cocktail regarding its clinical outcome are still limited, however, the rate of COVID-19-related hospitalization in our study was higher than the previous reports of REGN-COV2 treatment [24,25]. This could be due to the difference of background of enrolled patients including the type of variant of SARS-CoV-2 and risk factors for severe COVID-19. Verderese JP et al. also reported that there was a trend of increasing hospitalization rates as days from onset of symptoms to infusion were delayed [24]. It should be noted that, in our study, the percentage of patients who received the treatment early was relatively small and 49% of the patients received the treatment after 5 days of onset. Overall, no adverse events due to the infusion of the drug were noted, and the antibody cocktail therapy was beneficial in reducing the risk of severe or critical disease.

Second, patients who had completed the COVID-19 vaccination series before receiving the antibody cocktail did not develop severe illness. Both the Pfizer and Moderna vaccines have been shown to be effective in preventing severe disease [26,27], although deaths due to COVID-19 pneumonia after vaccinations have also been reported [28]. The REGN-COV2 antibody cocktail might be still beneficial in preventing COVID-19-related hospitalization in vaccinated patients. Importantly, the combination of COVID-19 vaccination and treatment with the antibody cocktail may be a key to combating COVID-19.

Finally, in our study, univariate analysis revealed that SpO_2 93–95% (room air) at the time of treatment (p = 0.004), CRP level (p < 0.001), LDH level (p < 0.001), IFN-λ3 level (p < 0.001), and presence of pneumonia on radiography (p = 0.039) were significantly associated with the need for COVID-19-related hospitalization. Notably, the rate of COVID-19-related hospitalization was 0% in the no risk group (0–1 abnormal data). Additionally, among the patients in the risk group (2–3 abnormal data), SpO_2 93–95% (room air) at admission, and high level of CRP and IFN-λ3 could be an indication for COVID-19-related hospitalization. Patient factors such as background characteristics or underlying conditions did not seem to affect the outcome. Regardless of the timing of the administration of the antibody cocktail, signs of inflammation were found to be a risk factor for the need for COVID-19-related hospitalization. This may be a clue for selecting patients who need more careful monitoring for exacerbation of COVID-19 after treatment with the REGN-COV2 antibody cocktail. Blood test and radiographic evaluation in addition to assessments of vital signs, especially SpO_2, are recommended in patients treated with the REGN-COV2 antibody cocktail.

There are some limitations in our study. First, this is a retrospective observational study of COVID-19 patients who were treated with REGN-COV2 without a control group. As such, it is difficult to compare the effect of the REGN-COV2 antibody cocktail to patients at high risk without the treatment. Secondly, we determined that, the number of patients was too small to perform a multivariate analysis for factors associated with the need for COVID-19-related hospitalization. Finally, it is difficult to remove confounding factors completely such as the effect

of vaccination, therefore the results of our study might not be the true effect of REGN-COV2.

5. Conclusion

Our study shows that the antibody cocktail consisting of casirivimab and imdevimab is a safe and beneficial treatment for patients at a high risk of severe and critical COVID-19. Recently, more patients have been receiving early treatment with the REGN-COV2 antibody cocktail in an outpatient setting in Japan. We hope that our findings will greatly contribute to the treatment of COVID-19.

Authorship statement

Ayana Sakurai and Shoko Marshall collected and analyzed the data and wrote the manuscript. Shoko Marshall contributed to the conception and design of the study. Tetsuya Ogawa supervised and validated the study. All authors revised the manuscript and approved the manuscript to be published.

Declaration of competing interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jiac.2022.03.029.

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