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Journal of Infection and Chemotherapy 28 (2022) 1459–1463

Contents lists available at ScienceDirect

Journal of Infection and Chemotherapy

journal homepage: www.elsevier.com/locate/jic

Original Article

Timing of REGEN-COV administration and progression to severe COVID-19

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ARTICLE INFO

Keywords:
REGEN-COV
COVID-19
Timing of administration
Severe disease
Epidemiology

ABSTRACT

Introduction: Several clinical trials have demonstrated that REGEN-COV (casirivimab and imdevimab) decreases the risk of hospitalization and death among COVID-19 patients. However, these trials did not evaluate the optimal timing of its administration, and evidence is limited regarding the relationship between the timing of administration and progression to severe COVID-19 among patients who receive REGEN-COV in a real-world setting. We examined the association between the timing of REGEN-COV administration and progression to severe COVID-19 among patients who received REGEN-COV in Japan.

Methods: We included a total of 342 COVID-19 patients (37 hospitals) who received REGEN-COV between July 19 and September 30, 2021. We calculated the difference between the date of symptom onset and the date of administration as an indicator of the timing of REGEN-COV administration and determined progression to severe COVID-19 after REGEN-COV administration. We conducted a logistic regression analysis, adjusting for potential confounders.

Results: The proportion of cases progressing to severe COVID-19 increased daily from symptom onset and sharply increased from day 5 of onset. The early administration (days 0–4) decreased the risk of progression to severity compared with late administration (after day 5), with an adjusted odds ratio of 0.29 (95% confidence interval: 0.11–0.56).

Conclusions: The early administration of REGEN-COV was associated with a decreased risk of progression to severe COVID-19 when the delta variant was dominant. The present epidemiological findings indicate that this monoclonal antibody therapy should be implemented very early in the clinical course probably even for emerging variants such as omicron BA.2.

1. Introduction

The global coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory coronavirus 2 (SARS-CoV-2), is ongoing and constitutes a global health threat. More than 6.12 million people have died from COVID-19 worldwide owing to its poor prognosis and high mortality [1,2]. Thus, it is important to prevent COVID-19 patients from progressing to severe disease, and antibody therapy is recommended for those who are at high risk of disease progression [3].

REGEN-COV (casirivimab and imdevimab) is a monoclonal antibody therapy that combines two neutralizing monoclonal antibodies. It was authorized for the treatment of patients with mild-to-moderate COVID-19 who are at high risk of progressing to severe COVID-19 when the delta variants was the mainstream [4–7]. Several clinical trials have demonstrated that REGEN-COV decreases the risk of hospitalization and death among COVID-19 patients [8,9]. These trials evaluated the efficacy and safety of the drug, but they did not evaluate the optimal timing of its administration. Although monoclonal antibody therapy is generally recommended to be started within 7 days of symptom onset [3], evidence is limited regarding the relationship between the timing of administration and progression to severe COVID-19 among patients who receive REGEN-COV in a real-world setting.

In the present study, we examined the association between the timing of REGEN-COV administration and progression to severe COVID-19 among patients who received REGEN-COV in Japan where it was approved in July 2021 [5]. The delta variant was dominant at that time in Japan.

Abbreviations: COVID-19, coronavirus disease 2019; CI, confidence interval; OR, odds ratio; REGEN-COV, casirivimab and imdevimab.

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https://doi.org/10.1016/j.jiac.2022.07.002
Received 16 April 2022; Received in revised form 15 June 2022; Accepted 4 July 2022
Available online 8 July 2022

2. Material and method

2.1. Study participants

We included COVID-19 patients who received REGEN-COV during the study period between July 19 and September 30, 2021, in Okayama, Japan. During the study period, more than 90% of COVID-19 patients in Okayama were infected with the delta variant [10]. The Okayama prefectural government sent questionnaires to all hospitals in Okayama Prefecture (37 hospitals) that treated patients with REGEN-COV during the study period based on the recommendation for REGEN-COV administration (i.e., the drug should be administered for mild to moderate patients who are at high risk for progression to severe COVID-19). The questionnaire inquired about patient characteristics such as age, sex, underlying diseases, symptoms, and clinical findings at the time of drug administration, as well as their prognosis after REGEN-COV administration.

This study was approved by the Institutional Review Board of Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences (No. 2201–014), which exempted requirement for informed consent because this was a retrospective study and complete anonymity was ensured. We conducted in compliance with the Declaration of Helsinki.

2.2. Timing of REGEN-COV administration

We calculated the timing of REGEN-COV administration as the difference between the date of symptom onset and the date of administration. The date of onset was defined as the date on which the patient first experienced any symptoms (such as cough, fever, or malaise) after infection. We then classified the timing of administration as early and late administration (0–4 days vs. ≥5 days after onset) on the basis of the distribution of the administration timing and in accordance with a previous report from the Tokyo Metropolitan Government, which demonstrated that early administration (0–4 days after the symptom onset) was associated with better prognosis compared to late administration (≥5 days) in a crude analysis [11].

2.3. Progression to severe COVID-19 after REGEN-COV administration

Progression to severe COVID-19 after administration was the outcome of interest. The questionnaire inquired about disease severity classification after administration (mild, moderate I, moderate II, severe) based on the COVID-19 guidelines published by the Ministry of Health, Labour and Welfare Japan [12]. The guidelines define the severity classification by a combination of respiratory symptoms and oxygenation. We then considered the patients who had a severity classification of moderate II (i.e., oxygen saturation in ambient air (SpO2) ≤ 93% and requiring supplemental oxygen) or above after administration as those proceeded to severe COVID-19 and classified the patients into two groups—those who proceeded to severe COVID-19 vs. those who did not.

2.4. Covariates

We dichotomized each potential confounding variable as follows except age (continuous): obesity (body mass index <30 vs. ≥30 kg/m^2); smoking status (non-smoker vs. smoker); underlying diseases (presence vs. absence); and vaccination status (completed vs. not-completed). We considered that patients had an underlying disease when they had any of the following: heart disease, chronic pulmonary disease, diabetes mellitus, chronic kidney disease, chronic hepatitis, immunosuppressed status (e.g., anticancer drug therapy, immune deficiency), and dyslipidemia. We defined the completed vaccination status as the passage of 2 weeks after the second dose of vaccine. We selected these variables on the basis of previous studies and knowledge of the risk factors for severe COVID-19 [13–18].

2.5. Statistical analysis

We first described the proportion of patients progressing to severe COVID-19 depending on the timing of REGEN-COV administration. We then compared baseline characteristics between the early and late administration groups (i.e., 0–4 days vs. ≥5 days after symptom onset).

To evaluate the associations between the timing of administration and progression to severe COVID-19, we conducted a logistic regression analysis using the late administration group as a reference. In Model 1, we estimated the crude odds ratios (ORs) for progression to severe COVID-19 with their 95% confidence intervals (Cls). We then adjusted for age (continuous) and sex in Model 2, and we further adjusted for obesity, smoking status, underlying diseases, and vaccination status in Model 3. We excluded cases with missing data and conducted our analysis only with cases that had complete data.

Because SpO_2 can easily fluctuate, some patients had $SpO_2 \leq 93\%$ at the time of administration. We thus performed the analyses including only patients with $SpO_2 \geq 94\%$ at the time of REGEN-COV administration to exclude those who were at high risk of becoming severe since the drug is recommended for use in patients who do not need supplemental oxygen. We also repeated the analysis after stratifying the patients by age (<40, 40–59, ≥60 years).

For the supplemental analysis, we conducted a cross-tabulation with Fisher's exact test to evaluate the relationship between the timing of administration and progression to severe COVID-19 among fully vaccinated (i.e., completed) patients.

We conducted all analyses with Stata statistical software (Stata SE version 17; Stata Corp LP, College Station, TX, USA).

3. Results

All of the hospitals returned the questionnaire, covering a total of 344 patients. Because REGEN-COV is generally recommended to be started within 7 days of symptom onset, we excluded two patients from the dataset because they were administered the drug after more than twice as long as recommended (i.e., 20 days and 3 months after symptom onset); thus, 342 patients were included in the analysis.

The distribution of the timing of administration and the proportion of patients progressing to severe COVID-19 depending on the timing of administration are shown in Fig. 1. Approximately 58% of the patients were given REGEN-COV within 0–4 days after symptom onset. The proportion of patients progressing to severe COVID-19 increased daily from symptom onset and increased sharply from day 5.

The baseline characteristics were similar between the early and late administration groups (0–4 days vs. ≥5 days after symptom onset); however, more patients in the late administration group were in the lower SpO_2 category and had pneumonia at administration (Table 1).

The results of the logistic regression analyses are shown in Table 2. Even after adjusting for the potential confounders (Model 3), early administration was associated with a decreased risk of progression to severe COVID-19 compared with late administration, with ORs of 0.25 (95% Cl: 0.11–0.56) for all patients and 0.29 (95% Cl: 0.12–0.70) for those with $SpO_2 \geq 94\%$ at administration.

When we stratified the patients by age category (Table 3), the decreased risks of early administration were observed among the patients older than 40 years of age.

In the supplemental analysis among 52 fully vaccinated patients, none of the patients in the early administration group proceeded to severe COVID-19 (0 of 35 patients), while three cases in the late administration group proceeded to severe COVID-19 (3 of 17 patients, 17.7%). Fisher's exact test gave p value of 0.03.

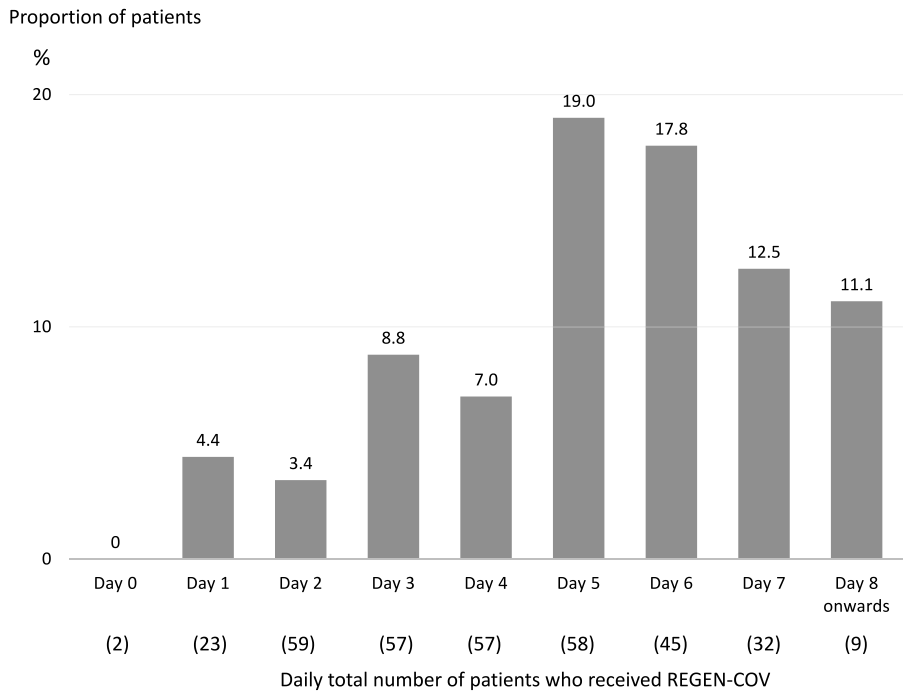

Fig. 1. Proportion of the patients who proceeded to severe COVID-19 after REGEN-COV administration at each day. The number in parentheses on the horizontal axis represents the daily total number of patients who received REGEN-COV.

Table 1
Demographic characteristics of COVID-19 patients who received REGEN-COV, categorized by time of administration (N = 342).

	Early administration Days 0–4 (n = 198) n (%)	Late administration After 5 day (n = 144) n (%)	p-value[a]
Sex			
Male	117 (59.1)	86 (59.7)	0.907
Female	81 (40.9)	58 (40.3)	
Age categories			
<40	31 (15.7)	17 (11.8)	0.006
40-59	85 (42.9)	87 (60.4)	
≥60	82 (41.4)	40 (27.8)	
Obesity			
BMI<30	121 (73.3)	100 (82.6)	0.063
BMI ≥ 30	44 (26.7)	21 (17.4)	
Smoking status			
Non-smoker	119 (60.1)	82 (56.9)	0.558
Smoker	79 (39.9)	62 (43.1)	
Underlying diseases			
No	57 (28.8)	55 (38.2)	0.067
Yes	141 (71.2)	89 (61.8)	
SpO2 at dosing			
<94	5 (2.5)	11 (7.6)	0.027
≥94	193 (97.5)	133 (92.4)	
Pneumonia			
No	95 (51.4)	27 (19.4)	<0.001
Yes	90 (48.7)	112 (80.6)	
Vaccination			
Completed[b]	35 (17.7)	17 (11.8)	0.135
Not-completed	163 (82.3)	127 (88.2)	

BMI, body mass index; COVID-19, coronavirus disease 2019; REGEN-COV, casirivimab and imdevimab.
The number of missing was 56 for obesity and 18 for pneumonia, respectively.
[a] The differences between the early and late administration groups were tested by the chi-square test.
[b] We defined vaccination completion as the passage of 2 weeks after receiving the second dose of vaccine.

Table 2
Associations between the timing of REGEN-COV administration and progression to severe COVID-19.

	case/N	Model 1:crude OR (95% CI)	Model 2[a] OR (95% CI)	Model 3[b] OR (95% CI)
Progression to severe COVID-19 (After dosing)				
Total cases of analysis		N = 342	N = 342	N = 286
After 5 day	24/144 (16.7)	1(Reference)	1 (Reference)	1 (Reference)
Days 0–4	12/198 (6.1)	0.32 (0.16–0.67)	0.28 (0.13–0.59)	0.25 (0.11–0.56)
Progression to severe COVID-19 (After dosing but with SpO2≥94% at dosing)				
Total cases of analysis		N = 326	N = 326	N = 271
After 5 days	18/133 (13.5)	1(Reference)	1 (Reference)	1 (Reference)
Days 0–4	9/193 (4.7)	0.31 (0.14–0.72)	0.28 (0.12–0.66)	0.29 (0.12–0.70)

COVID-19, coronavirus disease 2019; CI, confidence interval; OR, odds ratio; REGEN-COV, casirivimab and imdevimab.
[a] Adjusted for sex and age (continuous).
[b] Adjusted for sex, age (continuous), obesity, smoking status, underlying diseases, and vaccination.

4. Discussion

In the present study, we examined the association between the timing of REGEN-COV administration and progression to severe COVID-19 among patients who received the drug in Okayama, Japan. We found that compared with late administration, early administration decreased the risk of progression to severe disease.

In this study, the proportion of patients progressing to severe COVID-19 increased daily from symptom onset and steeply increased from day 5 after symptom onset. Early administration (days 0–4) was associated

Table 3
Associations between the timing of REGEN-COV administration and progression to severe COVID-19, stratified by age category.

	Progression to severe COVID-19	
	Case/N (%)	Adjusted OR (95% CI)[a]
<40 years old		
After 5 day	0/17 (0.0)	1(Reference)
Days 0–4	0/31 (0.0)	Not estimatable
40–59 years old		
After 5 day	15/87 (17.2)	1(Reference)
Days 0–4	6/85 (7.1)	0.37 (0.13–1.05)
≥60 years old		
After 5 day	9/40 (22.5)	1(Reference)
Days 0–4	6/82 (7.3)	0.15 (0.04–0.62)

COVID-19, coronavirus disease 2019; CI, confidence interval; OR, odds ratio; REGEN-COV, casirivimab and imdevimab.

[a] Adjusted for sex, age (continuous), obesity, smoking status, underlying diseases, and vaccination.

with better outcomes compared with late administration (on or after day 5). The findings support the current treatment guidelines from the National Health Institute and others [3,12] that emphasize the benefit of early administration. A previous study from US included a total of 270 patients treated with REGEN-COV and did not find difference in effectiveness between early (<3 days) and late (≥3 days) administration groups [22]. The different cutoffs, different number of the patients, or biases such as misclassification for symptom onset may explain the different findings, but the present study provides the useful information for timing of the administration of REGEN-COV.

COVID-19 pathogenesis includes two main processes: the replication of SARS-CoV-2 early in the clinical course and a dy sregulated immune/inflammatory response to SARS-CoV-2 that leads to tissue damage later in the clinical course [3]. Antibody therapy is thought to be effective because it prevents the virus from multiplying before the levels of neutralizing antibodies are able to increase in the body [19–21]. This possible mechanism explains why early administration leads to better outcomes.

A decreased risk of early administration was also observed in the supplemental analysis when we restricted the participants to those who completed vaccination. Although the analysis is preliminary because of the small sample size, the present findings support the treatment guidelines [3] that state that prior receipt of a vaccine should not affect treatment decisions.

The strengths of the present study are that all of the hospitals surveyed by Okayama prefectural government provided the required data and the study participants covered most of the patients who were administered REGEN-COV during the study period.

This study also has some limitations. First, the data were collected from multiple hospitals, and there are concerns regarding the misclassification of variables. In particular, the judgment of progression to severe COVID-19 depends on each doctor in the hospitals, but the misclassification would be minimal because there is the guideline for COVID-19 to define the severity. Second, it is possible that the timing of administration was misclassified in some cases because the date of symptom onset depended on the patients' self-report. Third, although we adjusted for potential confounders in the analyses, residual confounding is still possible because of unmeasured factors. Indeed, there were 56 missing cases (16% of the total number) for the variable of obesity, which might be a concern for the residual confounding. Finally, no one younger than 40 years of age progressed to severe disease, we therefore could not evaluate the effect among this group.

In conclusion, we demonstrated that the early administration of REGEN-COV decreased the risk of progression to severe COVID-19 during the study period when the delta variant was dominant. REGEN-COV is not recommended to use due to low neutralizing activity against the omicron (B.1.1.529) [23], but an in vitro study demonstrated that neutralizing activity of REGEN-COV was maintained against the omicrons/BA.2 [24]. The present epidemiological findings indicate that monoclonal antibody therapy should be implemented early in the clinical course probably even for emerging variants such as omicron BA.2.

Funding

This work was supported by Okayama Prefecture for investigating the COVID-19 outbreak [grant no. 7402000035].

Authorship statement

TK analyzed the data and wrote the first draft. SI, NM, ST, and TY contributed to the design of the study, interpreted the data, and revised the manuscript. All authors read and approved the final manuscript.

Declaration of competing interest

None.

Acknowledgments

We thank the medical institutions that provided the data, and Satoshi Mitsui, Yukari Takahashi, Saori Irie, and Yoko Oka for their cooperation in data collection. They are not a funding source and no conflict of interest. We thank Katherine Thieltges from Edanz (https://jp.edanz.com/ac) for editing a draft of this manuscript.

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