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# Clinical Effectiveness of REGN-COV2 in Patients with COVID-19 in Japan: A Retrospective Cohort Study with a Bayesian Inference

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No conflicts of interest.

## ABSTRACT

**Background:** Neutralizing antibody cocktail therapy, REGN-COV2, is promising in preventing a severe form of coronavirus disease 2019 (COVID-19), but its effectiveness in Japan has not been fully investigated.
**Materials and Methods:** To evaluate the effectiveness of REGN-COV2, clinical data of 20 patients with COVID-19 who received REGN-COV2 was compared with the control by matching age and sex. The primary outcome was the time from the onset to defervescence, the duration of hospitalization, and oxygen requirement. A sensitivity analysis using Bayesian analysis was also conducted.
**Results:** The time to defervescence was significantly shorter in the treatment group (5.25 *vs.* 7.95 days, $P = 0.02$), and so was the duration of hospitalization (7.115 *vs.* 11.45, $P = 0.0009$). However, the oxygen therapy requirement did not differ between the two groups (15% *vs.* 35%, $P = 0.27$). For Bayesian analysis, the median posterior probability of the time to defervescence since the symptom onset on the REGN-COV2 group was 5.28 days [95% credible interval (CrI): 4.28 - 6.31 days], compared with the control of 7.99 days (95% CrI: 6.81 - 9.24 days). The posterior probability of the duration of the hospitalization on the REGN-COV2 group was 7.17 days (95% CrI: 5.99 - 8.24 days), compared with the control of 11.54 days (95% CrI: 10.28 - 13.14 days). The posterior probability of the oxygen requirement on the REGN-COV2 group was 18% (95% CrI: 3 - 33%), compared with the control of 36% (95% CrI: 16 - 54%).
**Conclusion:** REGN-COV2 may be effective in early defervescence and shorter hospitalization. Its effectiveness for preventing a severe form of infection needs to be evaluated by further studies.

**Keywords:** Coronavirus disease 2019; REGN-COV-2; Bayesian statistics; Markov Chain Monte Carlo method

## INTRODUCTION

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) poses a significant burden both globally and in Japan [1]. The majority of patients develop a mild or asymptomatic infection, but a small proportion of

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**Author Contributions**

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mildly ill patients subsequently develops hypoxia and requires hospitalization with oxygen support [2-4]. Those patients with hypoxia tend to need a lengthy hospital stay and may end up with death after weeks of critical care [5]. Therefore, the method to prevent the development of a severe form of COVID-19 is eagerly wanted.

REGN-COV2 (Regeneron Pharmaceuticals, Inc., Westchester, NY, USA) is an antibody cocktail containing two SARS-CoV-2-neutralizing antibodies and was recently approved by the ministry of health and labor of Japan as a special occasion, to prevent a severe form of the infection with hypoxia. REGN-COV2 consists of two non-competing neutralizing human immunoglobulin G that target the receptor-binding domain of the SARS-CoV-2 spike protein, and prevent the virus from entering human cells [6, 7]. A preprint clinical trial demonstrated that a decrease in hospitalization and all-cause mortality among the patients with COVID-19 who were treated at the outpatient settings [8]. However, the clinical effectiveness of the medication has not been investigated in settings of Japan.

We here conducted a retrospective cohort study in investigating the clinical effectiveness of REGN-COV2 for the patients with COVID-19 in Japan, by applying Bayesian statistics using the Markov chain Monte Carlo (MCMC) method.

## MATERIALS AND METHODS

### 1. Participants

The patients diagnosed as COVID-19 and admitted to Hyogo Prefectural Kakogawa Medical Center, a medical center with designated COVID-19 wards, were screened for the analysis. Those patients who received REGN-COV2 were designated as *the Treatment* group. The criteria to administer REGN-COV2 is according to, but not limited to, the inclusion criteria in the package insert of RONAPREVE (the Japanese brand name) in Japan (https://www.info.pmda.go.jp/go/pack/62505A0A1023_1_01/). The inclusion criteria are shown below.

1. Positive SARS-CoV-2 antigen or polymerase chain reaction (PCR) tests of the specimens taken from either nasal, nasopharyngeal, oropharyngeal areas, or saliva, within 72 hours prior to the enrollment.
2. Compatible symptoms onset no more than 7 days before the administration.
3. Oxygen saturation level at room air is more than 93%.
4. The patient has at least one of the risk factors shown below.
   - The age ≥50 years old.
   - Obesity with body mass index (BMI) ≥30 kg/m$^2$.
   - Cardiovascular diseases including hypertension.
   - Chronic lung diseases including asthma.
   - Diabetes mellitus either type 1 or 2.
   - Chronic kidney disease including those on hemodialysis.
   - Chronic liver failure.
   - Immunosuppressed status, including those on chemotherapy, organ transplants, poorly controlled human immunodeficiency virus infection, sickle cell anemia, thalassemia, long term use of immunosuppressive medication.

According to these criteria, the treatment patients received a dose of REGN-COV2 consisting of a cocktail of two monoclonal antibodies, casirivimab 600mg and imdevimab 600 mg intravenously.


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We included all patients who received REGN-COV2 starting from July 24 until August 14, 2021. As *the Control*, we first screened all patients who were admitted to the center from April 1 until August 14, 2021, who suffice the inclusion criteria to provide REGN-COV2 but did not receive it. We further matched them to the Case by age and sex, with the ratio of 1: 1.

## 2. Study model

The primary outcome was the time to reach defervescence from the onset of the symptoms. Defervescence was defined as a measured body temperature of 37.5°C or lower for 24 hours, and the day they achieved the temperature was set as the time of defervescence. The secondary outcome was the duration of the hospitalization, requirement of oxygen therapy either nasal canula, high flow nasal cannula oxygenation, or mechanical ventilation.

We initially used Wilcoxon rank sum test for continuous variables, and Fisher exact test for a categorical variable to see the difference between REGN-COV2 group and the control.

In addition, as a sensitivity analysis, we constructed Bayesian models as follows: we assumed Poisson distribution for the primary outcome and the duration of hospitalization. We also assumed a Bernoulli distribution for the requirement of oxygen therapy. The precise expressions of our models are as follows.

$$X_{1i} \sim \text{Poisson}(\lambda_1) \text{ for } i=1,2,\ldots,N_1$$

$$X_{2i} \sim \text{Poisson}(\lambda_2) \text{ for } i=1,2,\ldots,N_2$$

$$\delta = \lambda_2 - \lambda_1$$

$$X_{1i} \sim \text{Bernoulli}(p_1) \text{ for } i=1,2,\ldots,N_1$$

$$X_{2i} \sim \text{Bernoulli}(p_2) \text{ for } i=1,2,\ldots,N_2$$

$$\delta = p_2 - p_1$$

Here X denotes derived probability on both groups, λ, and p are parameters, and δis the difference between the two groups.

We assumed a non-informative distribution for the prior of each parameter. From the data provided from the patients, the posterior distributions of parameters were obtained by the MCMC method. We set 4 separate sampling sequences, each consisting of 1,000 random samples (including 500 samples discarded for convergence). Sampling convergence was evaluated by Gelman-Rubin statistics and by visually inspecting a trace plot. The region of practical equivalence (ROPE) was arbitrarily determined from -2 to 2 for the time to defervescence and the duration of hospitalization. Likewise, ROPE was determined from -0.1 to 0.1 for the oxygen requirement. The null value is declared to be rejected if the 95% highest density interval (HDI) falls completely outside the ROPE, and the null value is declared to be accepted if the 95% HDI falls completely inside the ROPE.

Because of the arbitrary nature of the determined ROPE in our study, sensitivity analyses were performed using different numbers from -1 to 1, and from -3 to 3 for the primary outcome and the duration of hospitalization. ROPE of -0.2 to 0.2 was also set for the oxygen requirement. All 95% credible intervals (CrIs) were calculated using HDI.


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We used the R software program, version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria) with a probabilistic programming language Stan (Stan development team) for all Bayesian analyses.

This study was approved by the ethics committee of Hyogo Prefectural Kakogawa Medical Center (Approval number, 2021-33).

## RESULTS

A total of 20 patients received REGN-COV2 during the study period and all were included in the analysis as the treatment group. The flow diagram in including the patients are shown on **Fig. 1**. A total of 44 patients sufficed the criteria to be included as the control. The average age of the treatment group was 49 years old and one of the control candidates was 62 years old. After matching by age and sex, 20 patients were selected as the control with an average age of 48 years old. All patients included in the analyses did not receive any form of COVID-19 vaccines. The characteristics of the treatment and the control are shown in **Table 1**. There were no statistical differences between the two groups.

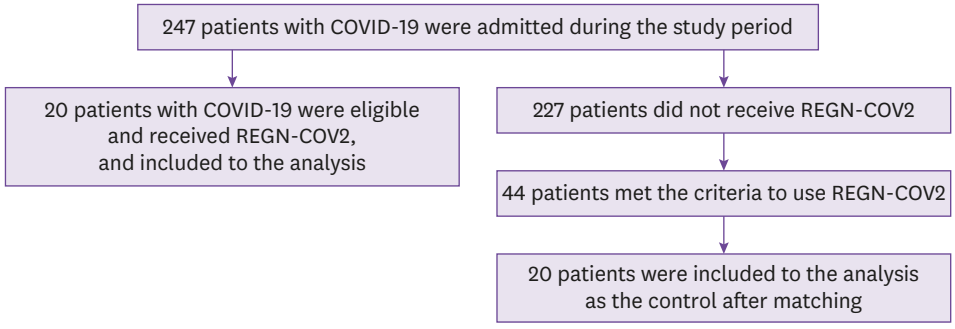


**Figure 1.** The flow diagram to show the patient's inclusion in the analysis.
COVID-19, coronavirus disease 2019.

**Table 1.** Patient characteristics on admission

| Characteristics n, (%) | REGN-COV2 | Control | *P*-value |
|---|---|---|---|
| Number of the patients | 20 | 20 | |
| Age (mean, range) | 49.0 (23 - 62) | 48.0 (22 - 63) | 0.82 |
| Female sex | 6 (30) | 8 (40) | 0.74 |
| Risk factors | | | |
| Age ≥50 | 13 (65) | 8 (40) | 0.21 |
| BMI ≥30 kg/m$^2$ | 6 (30) | 3 (15) | 0.45 |
| CVD | 9 (45) | 12 (60) | 0.53 |
| CLD | 3 (15) | 3 (15) | 1.0 |
| CKD | 6 (30) | 6 (30) | 1.0 |
| DM | 11 (55) | 6 (30) | 0.21 |
| CLF | 11 (55) | 13 (65) | 0.75 |
| Immunosuppression | 1 (5) | 3 (15) | 0.61 |
| Charlton comorbidity index (median, range) | 1 (0 - 3) | 1 (0 - 7) | 0.51 |
| Mean time from the onset to hospitalization (days, range) | 2.35 (1 - 4) | 3.10 (1 - 7) | 0.15 |
| Mean body temperature (°C, Range) | 37.4 (37.0 - 38.1) | 37.3 (36.0 - 38.3) | 0.61 |
| Oxygen saturation | 96.7 (93.0 - 99.0) | 97.0 (95.0 - 99.0) | 0.61 |
| BMI (kg/m$^2$, range) | 26.8 (18.4 - 33.3) | 25.4 (16.6 - 47.8) | 0.46 |
| WBC count (/mm$^3$, range) | 4,972 (3,080 - 7,330) | 5,346 (2,490 - 9,820) | 0.43 |
| CRP (mg/dL, range) | 1.46 (0.15 - 4.87) | 2.28 (0.07 - 8.53) | 0.28 |

CVD, cardiovascular diseases; CLD, chronic lung diseases; CKD, chronic kidney disease; DM, diabetes mellitus. CLF, chronic liver failure; BMI, body mass index; WBC, white blood cell; CRP, C-reactive protein.


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**Table 2.** Major outcomes between REGN-COV2 group and the control.

| Outcomes | REGN-COV2 (n = 20) | Control (n = 20) | *P*-value |
|---|---|---|---|
| Days to defervescence (mean days, range) | 5.25 (3 - 8) | 7.95 (0 - 22) | 0.02 |
| Duration of hospitalization (mean days, range) | 7.15 (3 - 15) | 11.45 (4 - 23) | 0.0009 |
| Oxygen requirement (number, percentage) | 3 (15%) | 7 (35%) | 0.27 |

The time to defervescence was significantly shorter in the treatment group (5.25 *vs.* 7.95 days, $P = 0.02$), and so was the duration of hospitalization (7.115 *vs.* 11.45, $P = 0.0009$). However, the oxygen therapy requirement did not differ between the two groups (15% *vs.* 35%, $P = 0.27$) (**Table 2**).

Bayesian inference as a sensitivity analysis revealed that the median posterior probability of the time to defervescence since the symptom onset on the treatment group was 5.28 days (95% CrI: 4.28 - 6.31 days), compared with the control of 7.99 days (95% CrI: 6.81 - 9.24 days) (**Fig. 2**). Regarding HDI, 15.22% fell inside the ROPE. A sensitivity analysis showed it became 0% for ROPE ranging from -1 to 1, and it became 66.37% when ROPE ranged from -3 to 3.

The posterior probability of the duration of the hospitalization on the treatment group was 7.17 days (95% CrI: 5.99 - 8.24 days), compared with the control of 11.54 days (95% CrI: 10.28 - 13.14 days) (**Fig. 3**).

Regarding HDI, 0% fell inside the ROPE. A sensitivity analysis showed it again became 0% for ROPE ranging from -1 to 1, and it became 1.91% when ROPE ranged from -3 to 3.

For oxygen therapy requirements, the treatment group had 3 patients who required nasal cannula oxygen therapy, and the control group had 7 patients who required oxygen therapy, including one on the high flow nasal cannula. No one required mechanical ventilation.

The posterior probability of the oxygen requirement in the treatment group was 18% (95% CrI: 3 - 33%), compared with the control of 36% (95% CrI: 16 - 54%) (**Fig. 4**).

Regarding HDI, 23.9% fell inside the ROPE. A sensitivity analysis with ROPE ranging from -0.2 to 0.2 was 57.2%.

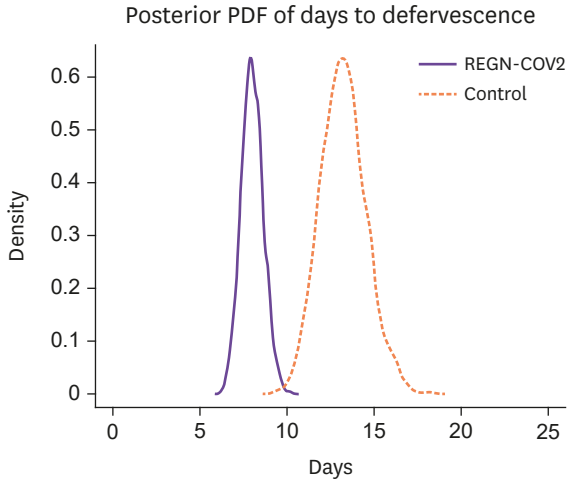


**Figure 2.** The posterior probability density function of time to defervescence.
PDF, probability density function.


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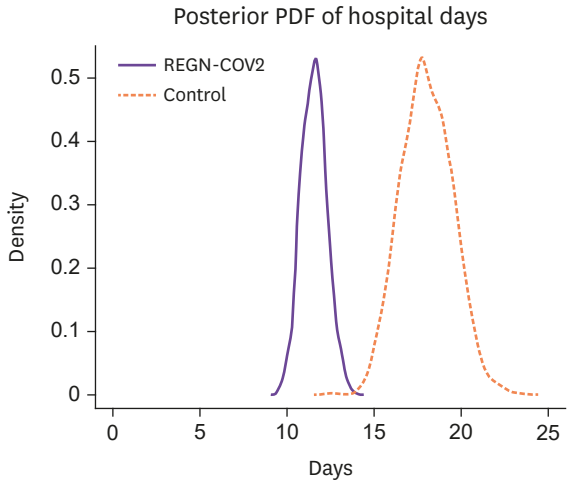


**Figure 3.** The posterior probability density function of the duration of hospitalization.
PDF, probability density function.

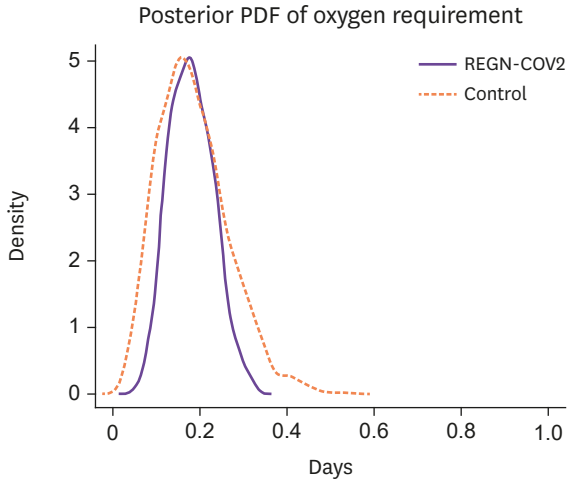


**Figure 4.** The posterior probability density function of the oxygen requirement.
PDF, probability density function.

Convergence was confirmed, with all values of Gelman-Rubin statistics being less than 1.1, and all trace plots also indicated convergence across four chains.

The median time from the administration of REGN-COV2 to defervescence was 2 days (range 1 - 3 days). No significant adverse effects were observed after the administration. All patients in both the treatment and control groups were discharged without in-hospital death.

## DISCUSSION

Our analyses suggested the superiority of REGN-COV2 therapy compared with the control. The treatment group was better both in the time to defervescence and the duration of hospitalization, although there was no difference in the oxygen treatment requirement. Even though this could come from the relatively small sample size of our cohort, our sensitivity analysis using Bayesian inference showed a similar result. The 95% credible interval did not


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overlap each other for the primary outcome, and ROPE was relatively small and even zero on the sensitivity analysis, suggesting that REGN-COV2 therapy is associated with faster resolution of fever. Likewise, the therapy also shortened the duration of the hospitalization with similar impacts on both the credible intervals and ROPE. The REGN-COV2 group also had fewer patients who required oxygen therapy, although our Bayesian analysis suggested that the posterior probability did not differ much compared with those without the therapy.

A preprint clinical trial suggested that REGN-COV2 given at the outpatient setting decreases hospitalization and rapid resolution of symptoms [8]. With a larger dose, it also may be associated with lower mortality if given to hospitalized patients, according to another preprint article [9]. Although REGN-COV2 was approved to use only for the hospitalized patients in Japan during our study period, it later became available in the outpatient settings too, enabling us to prevent hospitalization of mild COVID-19. Reduction of both severe COVID-19 and its hospitalization benefits us of improving the capacity of the healthcare system in Japan, which has been jeopardized by the repeated surge of COVID-19 [10].

We were able to demonstrate that REGN-COV2 could lead to rapid resolution of clinical symptoms with earlier discharge but were not able to demonstrate the preventive effects regarding the requirement of oxygen. Further studies with different methodology might be needed to clarify this discrepancy compared with the previous study [8].

Our study does have several inherent limitations. First, our data are from a single center, and they might not be generalizable to the patients in the other settings. Second, although we matched the treatment group and the control by age and sex, and both had similar clinical characteristics, there might be undetected factors that may make them differ, and this could produce biases to confound our findings. Because we aimed at finding the effectiveness of REGN-COV2 at the early stage of its provision, our cohort became relatively small and we were not able to adjust many potential confounding factors, our matching became rather arbitrary. However, there were no large differences between the treatment group and the control, and our Bayesian analysis demonstrated the clinical advantage of REGN-COV2, compared with the control, and its robustness suggests its clinical effectiveness. Third, there has been a change in the proportion of epidemiology of COVID-19 in Japan; namely the variants of concern. The delta variant, which is known to be more infectious to the other strains, and might be associated with a more severe form of infection, has become dominant during our study period [11, 12]. The change in the proportion of the variant may have affected the clinical outcome of our cohort. However, since we can assume that the group with the latter inclusion, which is REGN-COV2 group, has more delta variants than the group of the former inclusion, the control group, the difference is likely to affect negatively to the REGN-COV2 group. Therefore, the effectiveness of REGN-COV2 could rather be strengthened if the proportion of the variants were to be matched. Finally, we did not investigate the safety and the effectiveness of REGN-COV2 in a long run after the patients' discharge. Long COVID-19 could affect many infected patients and could occur even among mildly ill patients [13]. Further studies to elucidate the effectiveness of REGN-COV2 for a longer period should be conducted.

In conclusion, our Bayesian analysis with the MCMC method suggested that a cocktail antibody therapy, REGN-COV2, is likely to be associated with rapid resolution of fever among the patients with COVID-19 without hypoxia, and contribute to early hospital discharge in Japan. Its effectiveness in preventing hypoxia and severe COVID-19 needs further evaluation in similar settings.

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