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Early Oxygen Requirement in Patients with Mild-to-Moderate COVID-19 Who Received Regdanvimab after Delta-Variant Outbreak

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Conflict of Interest
No conflict of interest.

ABSTRACT

Background: Regdanvimab is a monoclonal antibody targeted against the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and a treatment option for patients with mild-to moderate coronavirus disease 2019 (COVID-19). However, there has been limited information on the clinical effectiveness of regdanvimab in the Delta variant of SARS-CoV-2. Therefore, we aimed to investigate the effectiveness of regdanvimab after the Delta variant was dominant using chronological analysis of regdanvimab use in a real-world setting.

Materials and Methods: The electrical medical records of patients infected with mild-to-moderate COVID-19 who received regdanvimab within 7 days of symptom onset were reviewed before (February – June 2021) and after (August – November 2021) the Delta variant became predominant in Korea. Clinical outcomes were assessed by the need for oxygen supplementation, time from symptom onset to oxygen requirement, in-hospital mortality, and length of hospitalization. To match the difference between the basic characteristics of the two groups, the clinical outcomes were compared again after 1 : 1 propensity score matching.

Results: Patients treated with regdanvimab in the Delta-predominant group were more likely to require oxygen supplementation (17.5% *vs.* 6.0%, *P* = 0.019) and had shorter times from symptom onset to supplemental oxygen use (mean ± standard deviation [SD]: 5.8 ± 2.8 *vs.* 10.0 ± 3.7, *P* = 0.007) than those in the control group. After propensity score matching, the percentage of patient requiring oxygen supplementation was higher (15.2% *vs.* 6.1%, *P* = 0.156), while the time from symptom onset to oxygen supplementation was significantly shorter in the Delta-predominant group (mean ± SD: 4.9 ± 2.1 *vs.* 10.0 ± 3.7, *P* = 0.007) than that in the control group.

Conclusion: Considering that high proportion of vaccinated patients in the Delta-predominant group, this finding suggests the uncertainty whether the effect of regdanvimab is maintained even during the Delta-predominant period. It is hence necessary to continuously monitor the effectiveness of regdanvimab as new SARS-CoV-2 variants emerge.

Keywords: SARS-CoV-2; Monoclonal antibody; Neutralizing antibody; Therapeutics; Mutation

Author Contributions
Conceptualization: EL. Data curation: EL. Formal analysis: CML, EL, SWP. Investigation: CML, EL, SWP. Methodology: CML, EL, SWP. Writing - original draft: CML. Writing – review & editing: EL, SWP.

INTRODUCTION

Since the first reported case of pneumonia due to coronavirus disease 2019 (COVID-19) in December 2019 [1], millions of people have been infected [2]. The causative agent is the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), and while most of the patients with SARS-CoV-2 infection have mild symptoms, some progress to severe disease that requires supplemental oxygen or even results in death [3, 4]. As the SARS-CoV-2 pandemic continues, various therapeutic agents have been developed.

Anti-SARS-CoV-2 monoclonal antibody is a treatment option for patients with mild-to-moderate COVID-19 [5]. Regdanvimab (CT-P59, Celltrion Inc, Incheon, Korea) is an anti-SARS-CoV-2 monoclonal antibody that has shown safety and virologic efficacy in a phase I study [6] and reduced progression of severe COVID-19 and time to recovery in a phase II/III clinical trial [7]. Based on the results of these previous studies, regdanvimab was approved for emergency use in Korea on February 5, 2021. Although regdanvimab is used for treating COVID-19 in clinical practice and its effectiveness in patients with mild-to-moderate COVID-19 has been investigated [8], there has been no study on the effectiveness of regdanvimab when the Delta variant of SARS-CoV-2 was dominant. As clinical trials and studies on the clinical effectiveness of regdanvimab were conducted before the Delta variant became predominant, the effectiveness of regdanvimab when the Delta is the dominant strain has been questioned.

Therefore, we aimed to investigate the effectiveness of regdanvimab after the Delta variant became predominant by comparing the treatment effectiveness before and after the Delta variant became predominant.

MATERIALS AND METHODS

1. Study setting and population

This retrospective study was conducted in a hospital designated for COVID-19 by the Seoul Metropolitan Government with 765 inpatient beds, including 195 nationally designated negative-pressure isolation units in Seoul, Korea. The indications for admission to this hospital in Korea have remained unchanged since 2020, and the admission criteria have been changed to be based on at-home treatment after November 30, 2021.

The progression of COVID-19 in patients who received regdanvimab was confirmed retrospectively based on information in their electronic medical records (EMR). The Delta-predominant group included patients who received regdanvimab in the study hospital from August 2021, when the Delta variant was confirmed as the dominant variant in Korea [9, 10], to November 2021 before the hospitalization criteria was changed by the government. The control group included patients who received regdanvimab from February to June 2021, the period before the Delta variant became dominant, in the same study hospital. The data of these patients were also presented in our previous study [8]. The number of patients who met the indication of regdanvimab but did not receive regdanvimab during the Delta-predominant study period were counted, and the need for oxygen supplementation among those patients was also collected.

Regdanvimab was approved for administration within 7 days of symptom onset to patients who met one of the following criteria: (1) age ≥60 years, (2) a confirmed diagnosis of

pneumonia by imaging tests, and (3) presence of comorbidities such as chronic respiratory disease, cardiovascular disease, hypertension, and diabetes mellitus. Therefore, patients who received regdanvimab more than 7 days after symptom onset were excluded from the study.

2. Ethics statement

This study was approved by the Institutional Review Board (IRB) of the Seoul Metropolitan Government Boramae Medical Center (No. 20-2021-53). The IRB waived the need for informed consent owing to the retrospective nature of this study.

3. Data collection and outcome measures

Data on the clinical characteristics of the enrolled patients were collected through an EMR review. Patients' age and sex; date of symptom onset; results of imaging tests including plain chest radiography and computed tomography; underlying diseases (hypertension, diabetes mellitus, cardiovascular disease, chronic respiratory disease, chronic kidney disease, malignancy, and immunosuppressive status); body mass index (BMI); COVID-19 vaccination status; supplemental oxygen therapy; in-hospital mortality; and length of hospital stay were investigated. The need for oxygen supplementation, time from symptom onset to supplemental oxygen therapy, in-hospital mortality, and length of hospital stay in days were confirmed as clinical outcomes following regdanvimab use.

4. Statistical analysis

The clinical characteristics and outcomes were compared between patients who received regdanvimab before (February – June 2021) and after (August – November 2021) the Delta variant became dominant [9, 10]. Student's t-test was used to compare continuous variables, and the chi-squared or Fisher's exact test were used to compare categorical variables. To minimize selection bias, subgroup analysis was performed using 1 : 1 propensity score (PS) matching for the variables, age, sex, BMI, underlying diseases, and chest radiography abnormalities. Vaccination status was excluded in PS matching because the large difference between two groups caused overestimation. Statistical significance was set at P <0.05. All statistical analyses except PS matching were performed using SPSS Statistics, version 26.0 (IBM Corp., Armonk, NY, USA). The PS matching was performed using R software, version 4.0.3 (R foundation for Statistical Computing, Vienna, Austria).

RESULTS

1. Patients' characteristics

A total of 257 patients received regdanvimab within 7 days of symptom onset after the Delta variant became dominant (August – November 2021). These patients were classified as the Delta-predominant group. The control group included 67 patients who received regdanvimab within 7 days of symptom onset before the Delta variant became dominant (February – June 2021).

The clinical characteristics of the patients in the Delta-predominant group and the control group are shown in **Table 1**. Patients in the control group were significantly older than those in the Delta-predominant group (mean ± standard deviation [SD]: 64.5 ± 14.5 *vs.* 59.8 ± 15.9, P = 0.029), while the proportion of male sex and BMI did not differ significantly between the two groups. Although a higher proportion of patients in the Delta-predominant group had malignancy than that in the control group (19.1% *vs.* 7.5%, P = 0.026), the proportion of patients with other underlying comorbidities did not differ significantly between the

Table 1. Clinical characteristics and treatment outcomes of patients who received regdanvimab before and after the Delta variant was dominant

	Delta-predominant (n = 257)	Control (n = 67)	P-value
Age (mean ± SD), years	59.8 ± 15.9	64.5 ± 14.5	0.029
Male sex	132 (51.4)	31 (46.3)	0.458
BMI (mean ± SD), kg/m²	23.5 ± 4.0	23.6 ± 4.0	0.758
Hypertension	98 (38.1)	33 (49.3)	0.099
Cardiovascular disease	40 (15.6)	7 (10.4)	0.336
Diabetes mellitus	47 (18.3)	14 (20.9)	0.603
Chronic pulmonary disease	21 (8.2)	6 (9.0)	0.806
Chronic kidney disease	22 (8.6)	5 (7.5)	>0.999
Malignancy	49 (19.1)	5 (7.5)	0.026
Immunosuppression	16 (6.2)	2 (3.0)	0.385
Chest radiography abnormality	148 (57.6)	33 (49.3)	0.221
Duration of symptoms before regdanvimab (mean ± SD), days	3.7 ± 1.9	3.8 ± 1.5	0.727
Vaccination status			
More than one COVID-19 vaccination	122 (47.8)	5 (7.5)	<0.001
Full COVID-19 vaccination	94 (36.9)	1 (1.5)	<0.001
Oxygen requirement	45 (17.5)	4 (6.0)	0.019
Duration of symptoms before oxygen requirement (mean ± SD), days	5.8 ± 2.8	10.0 ± 3.7	0.007
In-hospital mortality	4 (1.6)	0 (0.0)	0.584
Admission duration (mean ± SD), days	9.6 ± 5.4	10.9 ± 4.9	0.070

If not specified, the proportion was expressed in parenthesis.
SD, standard deviation; BMI, body mass index; COVID-19, coronavirus disease 2019.

two groups. The proportion of patients with chest radiography abnormalities was not significantly different between the Delta-predominant group and the control group (57.6% *vs.* 49.3%, *P* = 0.221). The duration of symptoms before regdanvimab treatment did not differ between the two groups. The proportion of patients who were vaccinated more than once and fully were significantly higher in the Delta-predominant group than in the control group (47.8% *vs.* 7.5%, *P* <0.001; 36.9% *vs.* 1.5%, *P* <0.001).

2. Treatment outcomes

The treatment outcomes of patients in the Delta-predominant and control groups are presented in **Table 1**. The proportion of patients who required supplemental oxygen therapy was significantly higher in the Delta-predominant group than in the control group (17.5% *vs.* 6.0%, *P* = 0.019), and the time from symptom onset to supplemental oxygen therapy was significantly shorter in the Delta-predominant group (mean ± SD: 5.8 ± 2.8 *vs.* 10.0 ± 3.7, *P* = 0.007). Although in-hospital mortality was not significantly different between the two groups, there were no deaths in the control group, while four (1.6%) in-hospital deaths occurred in the Delta-predominant group. The length of hospitalization did not differ between the two groups.

After 1 : 1 PS matching analysis, 66 patients in the Delta-predominant group and 66 patients in the control group were analyzed. The clinical characteristics and treatment outcomes of patients from both groups after PS matching analysis are shown in **Table 2**. As the vaccination status was excluded in PS matching, the proportion of patients who were vaccinated more than once and fully were higher in the Delta-predominant group than in the control group.

Although not statistically significant, the proportion of patients requiring supplemental oxygen therapy was higher in the Delta-predominant group than in the control group (15.2% *vs.* 6.1%, *P* = 0.156). The time from symptom onset to supplemental oxygen therapy remained significantly shorter in the Delta-predominant group than in the control group (mean ± SD: 4.9 ± 2.1 *vs.* 10.0 ± 3.7, *P* = 0.007). There was one (1.5%) in-hospital death in the Delta-

Table 2. Clinical characteristics and treatment outcomes of patients who received regdanvimab after propensity score matching

	Delta-predominant (n = 66)	Control (n = 66)	P-value
Age (mean ± SD), years	67.3 ± 13.4	64.2 ± 14.4	0.204
Male sex	33 (50.0)	31 (47.0)	0.728
BMI (mean ± SD), kg/m²	23.4 ± 3.7	23.6 ± 4.0	0.721
Hypertension	35 (53.0)	33 (50.0)	0.728
Cardiovascular disease	5 (7.5)	7 (10.6)	0.763
Diabetes mellitus	14 (21.2)	14 (21.2)	>0.999
Chronic pulmonary disease	3 (4.5)	6 (9.1)	0.744
Chronic kidney disease	3 (4.5)	5 (7.6)	0.718
Malignancy	9 (13.6)	5 (7.6)	0.397
Immunosuppression	0 (0.0)	2 (3.0)	0.496
Chest radiography abnormality	37 (56.1)	32 (48.5)	0.384
Duration of symptoms before regdanvimab (mean ± SD), days	3.7 ± 1.9	3.8 ± 1.5	0.618
Vaccination status			
More than one COVID-19 vaccination	39 (59.1)	5 (7.6)	<0.001
Full COVID-19 vaccination	31 (47.0)	1 (1.5)	<0.001
Oxygen requirement	10 (15.2)	4 (6.1)	0.156
Duration of symptoms before oxygen requirement (mean ± SD), days	4.9 ± 2.1	10.0 ± 3.7	0.007
In-hospital mortality	1 (1.5)	0 (0.0)	>0.999
Admission duration (mean ± SD), days	9.9 ± 5.2	10.9 ± 4.9	0.222

If not specified, the proportion was expressed in parenthesis.
SD, standard deviation; BMI, body mass index; COVID-19, coronavirus disease 2019.

Table 3. Proportions of patients with oxygen requirement according to the study period and whether receiving regdanvimab

	Regdanvimab	Symptomatic treatment	P-value
Pre-Delta period	4/67 (6.0)	67/333 (20.1)	0.006
Delta-predominant period	45/257 (17.5)	120/599 (20.0)	0.391

predominant group, and statistical calculations could not be conducted. In addition, there was no significant difference in the length of hospitalization (9.9 *vs.* 10.9 days, *P* = 0.222).

Among 2,508 patients admitted to the study hospital during the Delta-predominant study period, we exclude 431 patients who required oxygen therapy within 1 day after admission, 371 pediatric patients under 17 years of age, and 257 patients who received regdanvimab. Among 1,449 patients, total 599 patients met the indication of regdanvimab. The requirement of supplemental oxygen occurred in 120 patients of these 599 patients (**Table 3**). The proportion of oxygen requirement was not significantly different between the group receiving regdanvimab and the group not receiving regdanvimab during the Delta-predominant period (17.5% *vs.* 20.0%, *P* = 0.391).

DISCUSSION

We compared the effectiveness of regdanvimab in patients with COVID-19 before and after the Delta variant became predominant in Korea. We found that patients receiving regdanvimab in the Delta-predominant group had a shorter duration from symptom onset to supplemental oxygen therapy than those in the control group. Although previous studies reported that treatment with regdanvimab reduced the risk of progression to oxygen requirement [8, 11], these studies were conducted when the Delta variant was not dominant. After this study period, the prevalence of the Delta variant increased rapidly, and it became the predominant strain in Korea [9, 10].
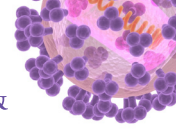
A previous study demonstrated the efficacy of regdanvimab against the Delta and other variants of SARS-CoV-2; however, the study was limited to *in vitro* and animal experiments [12]. Another study showed that bamlanivimab, another therapeutic monoclonal antibody used against COVID-19, did not have neutralizing activity against the Delta variant, and sera from vaccinated individuals had little to no activity against it [13]. The clinical effectiveness of regdanvimab during the Delta-predominant period may have been affected by the escape of this variant from the monoclonal antibody, as regdanvimab is directed against the spike protein of SARS-CoV-2.

This study found poor clinical outcomes in the Delta-predominant group. We found that the proportion of patients requiring supplemental oxygen therapy was higher, and the duration from symptom onset to supplemental oxygen therapy was shorter in the Delta-predominant group compared to the control group. The shorter duration of symptom onset to supplemental oxygen therapy in the Delta-predominant group showed statistical significance even after 1 : 1 PS matching analysis.

The virulence of Delta variant itself might contribute to the reduced effectiveness of regdanvimab during the Delta-predominant period. Therefore, we additionally analyzed patients who met the indication criteria for regdanvimab but were not treated with the drug during the Delta-predominant study period (August – November 2021), and confirmed the number of patients who require oxygen therapy among them. We found that there was no significant difference in the proportion of oxygen requirement between patients without regdanvimab and those with regdanvimab. Differently from this result, the previous study showed that clinical characteristics of patients without regdanvimab therapy during pre-Delta period and reported the lower proportion of patients with oxygen requirements among those receiving regdanvimab [8]. Although there have been previous reports of higher clinical severity of Delta variant than other variants [14, 15], percentage of patients with oxygen requirement between symptomatic treatment groups in Delta-predominat period and pre-Delta period was similar in the study hospital.

All physicians in this study hospital followed the international COVID-19 treatment guidelines [5], which advised against other than monoclonal antibody in mild to moderate COVID-19. Moreover, remdesivir is administered as an orphan drug by Korean government and it can be administered only when oxygen supplement is required due to the regulations by Korea Disease Control and Prevention Agency. Therefore, since the only treatment option for patients who did not require oxygen therapy was regdanvimab during this study period, there might be little effect of other treatments in both the Delta-predominant group and the control group.

These findings are consistent with those of a previous study conducted in the United States reporting the possibility of reduced monoclonal antibody effectiveness in a real-world setting during the Delta-predominant period [16]. As recent studies suggested reduced monoclonal antibody efficacy and neutralization by vaccinated serum of the new variant of concern, omicron [17, 18], we could expect that the clinical effectiveness of regdanvimab may decrease when other new variant becomes dominant, similar to the Delta variant.

This study has some limitations. First, as a retrospective cohort study, the clinical characteristics of the Delta-predominant group could not be exactly matched with those of the control group. Therefore, we used PS matching analysis for important clinical variables to

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minimize selection bias. Second, no microbiologic investigation of SARS-CoV-2 variants was conducted in this study. However, as we did not limit hospitalization to specific patients, it is expected that the proportion of specific variants in this study represents that of the general population in Korea.

In conclusion, this study demonstrates a shorter time from symptom onset to supplemental oxygen therapy in patients treated with regdanvimab during the Delta-predominant period. Although other factors of clinical outcome did not differ between the Delta-predominant group and the control group after 1 : 1 PS matching analysis, it was unclear whether the effectiveness of regdanvimab is maintained considering the SARS-CoV-2 vaccination status. As new variants of SARS-CoV-2 emerge, it would be important to continuously monitor the clinical effectiveness of regdanvimab.

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