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Original Article

Real World Experience with Regdanvimab Treatment of Mild-to-Moderate Coronavirus Disease-19 in a COVID-19 Designated Hospital of Korea

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ABSTRACT

Background: Real-world clinical data concerning regdanvimab, a monoclonal antibody treatment for patients with mild-to-moderate coronavirus disease 2019 (COVID-19), are urgently needed. Here, we describe our experience with regdanvimab.
Materials and Methods: This retrospective cohort study enrolled high-risk adults with mild-to-moderate COVID-19 who were admitted to a dedicated COVID-19 hospital in Korea from March to September 2021. We used multiple logistic regression and propensity score-matching to compare the outcomes of patients who did or did not receive regdanvimab. The primary outcome was in-hospital progression to severe or critical status, or death.
Results: Of 586 patients eligible for regdanvimab, 256 patients who received regdanvimab and 251 untreated patients were included. The median age was 66 years and 47.5% were men. The most common underlying illnesses were hypertension (53.8%) and diabetes (36.9%). Patients were admitted to the hospital at a median of 2 days after symptom onset; regdanvimab was administered at a median of 3 days after symptom onset. Multivariate analysis indicated that regdanvimab significantly reduced the risk of disease progression during hospitalization [odds ratio (OR): 0.285; 95% confidence interval (CI): 0.144 - 0.564]. In a 1:1 propensity score-matched cohort (172 patients in either group), regdanvimab also decreased the risk of progression (OR: 0.162; 95% CI: 0.068 - 0.386).
Conclusion: In high-risk patients with mild-to-moderate COVID-19, regdanvimab decreased the risk of progression to severe COVID-19.

Keywords: Regdanvimab; Monoclonal antibody; COVID-19

INTRODUCTION

Although more than 1 year has passed since the World Health Organization declared coronavirus disease 2019 (COVID-19) to be a global pandemic, hundreds of thousands of daily cases and thousands of daily deaths continue to be reported worldwide [1]. Most patients

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with mild-to-moderate COVID-19 recover without specific treatment, but approximately 8.0% to 30.0% eventually progress to severe or critical disease [2]. Risk factors for disease progression and poor outcomes include older age; cardiovascular, chronic lung, and chronic kidney disease; diabetes; obesity; cancer; and immunosuppression [3]. Neutralizing monoclonal antibodies have been developed for high-risk patients [4-8]. Regdanvimab (CT-P59, Celltrion, Incheon, Korea) is a monoclonal antibody that targets the receptor-binding domain of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein. A preclinical study in animals demonstrated a 100-fold reduction in viral load and the alleviation of clinical symptoms [9]. A Phase II/III clinical trial reported reduced progression to severe COVID-19 in 54.0% of patients with mild-to-moderate symptoms and 68.0% of patients with moderate symptoms aged >50 years, as well as significantly more rapid clinical recovery (3.4 to 6.4 days) than in placebo-treated patients [10]. Thus, regdanvimab received conditional approval for emergency use in February 2021, and full approval in September 2021, from the Korea Ministry of Food and Drug Safety (MFDS) [11]. The European Medicines Agency Committee has encouraged regdanvimab treatment for COVID-19 patients [12]. However, more real-world data concerning treatment effects and adverse events are required. Here, we describe our experience with regdanvimab.

MATERIALS AND METHODS

1. Study setting

This observational cohort study was conducted at Masan Medical Center (MMC), a 300-bed public hospital in Changwon, Gyeongsangnam-do Province (population 3.5 million), Korea. MMC has operated as a dedicated hospital for patients with mild-to-moderate COVID-19 since February 2020. During the study period, all adult COVID-19 cases were hospitalized immediately or transported to residential treatment centers for treatment and isolation. MMC provided treatment for patients who required low-flow oxygen therapy; severe or critical patients who required high-flow therapy or mechanical ventilation were transferred to university hospitals. Patients were discharged if they met the clinical or testing criteria of the Korean Government. In the clinical criteria, any symptomatic case must not have fever in the absence of fever reducers and other clinical symptoms must improve for at least 72 h after 10 days from symptom onset. Asymptomatic patients were discharged if they lacked any clinical symptoms for 10 days. The testing criteria required cases to be polymerase chain reaction test-negative twice, with at least 24 h between the tests [13].

2. Study design and participants

The indications for regdanvimab (Celltrion, as conditionally approved by the MFDS) were adults (age >60 years) with mild COVID-19 and at least one of diabetes mellitus, hypertension, cardiovascular disease, or chronic lung disease; or radiologically confirmed pneumonia (regardless of concomitant risk factors). To allow comparisons with other studies, we modified the clinical criteria based on the recommendations of the United States Food and Drug Administration (US FDA). Our clinical criteria were mild-to-moderate COVID-19 developing within 10 days of symptom onset, and at least one of age ≥65 years or diabetes mellitus; or age >55 years with hypertension, cardiovascular disease, or chronic lung disease. All consenting patients received a single intravenous infusion of 40 mg/kg regdanvimab over 90 min. Patients with severe COVID-19 received steroids and remdesivir. Regdanvimab became available at MMC on March 15, 2021. We included adults hospitalized from March 1, 2021, to September 30, 2021, with laboratory-confirmed (reverse transcriptase polymerase

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chain reaction) COVID-19 who met the above clinical criteria. We compared patients who received and did not receive regdanvimab. We reviewed medical records (demographics, chronic health conditions, COVID-19 vaccination status, symptoms, laboratory findings, and disease severity at admission). The disease severity at admission was classified based on the National Institute of Health guidelines: mild, symptoms and signs without evidence of lower respiratory tract disease; moderate, symptoms with radiologically confirmed pneumonia but no hypoxemia; severe, respiratory rate >30 breaths/min, oxygen saturation <94.0% on room air at sea level, PaO_2/FiO_2 <300 mmHg, or lung infiltrates >50.0%; Critical cases were patients who had respiratory failure, septic shock, and/or multiorgan failure [14]. Patients who had clinical manifestations of severe COVID-19 within 2 days of hospitalization and those who received both regdanvimab and oxygen (within 6 h after monoclonal antibody treatment) were excluded because regdanvimab was unlikely to exert any effects in such patients [15]. Patients with incomplete medical records were also excluded. The primary outcome was progression of asymptomatic-to-moderately ill COVID-19 patients to severe or critical status during hospitalization. The duration of hospitalization, transfers to university hospitals, and deaths during hospitalization were also evaluated.

3. Ethics statement

The study protocol was approved by the Gyeongsang National University Changwon Hospital Institutional Review Board (GNUCH no. 2021-07-039). Informed consent was waived because of the retrospective nature of the study.

4. Statistical analysis

Baseline characteristics are summarized using standard descriptive statistics. Continuous variables were compared using the Mann–Whitney U-test; categorical variables were compared using the χ^2 test or Fisher's exact test, as appropriate. Univariate analysis was performed to identify variables significantly associated with COVID-19 progression. All variables with *P*-values <0.1 on univariate analysis, and other significant parameters (vaccination status and regdanvimab treatment), were included in multivariate logistic regression to identify risk factors for disease progression. Physicians tended to prescribe the monoclonal antibody for patients with more severe symptoms (**Table 1**). Thus, we used propensity score-matching to adjust for differences in baseline characteristics; we sought to reduce selection bias and confounding. Nearest-propensity score-matching (without replacement; ratio 1: 1; and caliper = 0.25) between the treatment and control groups was based on age (<65 and ≥65 years); sex; body mass index (BMI) (BMI <30 and ≥30 kg/m^2); comorbidities (diabetes, hypertension, chronic lung disease, cerebrovascular disease, cardiovascular disease, or malignancy); COVID-19 severity; vaccination status; and body temperature and symptoms on admission. Comorbidities with <5 cases were not included. Covariate balances in the matched cohort were evaluated using standardized mean differences [16]. Additional multivariate logistic analysis was performed to identify risk factors for COVID-19 disease progression in the propensity score-matched cohort. Kaplan–Meier curves were drawn to compare the outcomes of the two groups using the log-rank test. To evaluate the effect of regdanvimab on SARS-CoV-2 B.1.617.2 (Delta) variants indirectly, subgroup analyses were performed with similar approaches by dividing before and after July 2021, when the Delta variant became dominant (the "fourth wave"). All tests were two-tailed, and a *P*-value <0.05 was considered statistically significant. All analyses were performed using SPSS software (version 24.0, IBM Corporation, Armonk, NY, USA) and R software (version 4.1.1 with the R packages; The R Project for Statistical Computing, Vienna, Austria).

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Table 1. Clinical characteristics and outcomes of COVID-19 patients before and after propensity score matching

Variables	Pre-matched cohort				Propensity score-matched cohort			
	Total (n = 507)	Regdanvimab (n = 256)	Control (n = 251)	*P*	Total (n = 344)	Regdanvimab (n = 172)	Control (n = 172)	*P*
Age (years)	66 (60 – 72)	66 (60 – 72)	67 (60 – 72)	0.646	67 (62 – 72)	66 (61 – 72)	67.5 (63 – 72)	0.479
Age ≥65 years	316 (62.3)	158 (61.7)	158 (62.9)	0.775	232 (67.4)	112 (65.1)	120 (69.8)	0.357
Male	241 (47.5)	122 (47.7)	119 (47.4)	0.956	159 (46.2)	80 (46.5)	79 (45.9)	0.914
BMI, kg/m^2	24.1 (22.1 – 26.2)	24.5 (22.6 – 26.4)	23.5 (21.5 – 25.6)	0.017	24.0 (22.2 – 26.2)	24.5 (22.6 – 26.6)	23.7 (21.9 – 25.9)	0.053
BMI ≥30 kg/m^2	22 (4.3)	12 (4.7)	10 (4.0)	0.698	11 (3.2)	6 (3.5)	5 (2.9)	0.999
Days from symptom onset								
To admission[a], median (range)	2 (0 – 9)	2 (0 – 8)	3 (0 – 9)	0.012	2 (0 – 9)	2 (0 – 8)	3 (0 – 9)	0.056
To Regdanvimab treatment, median (range)	3 (0 – 9)	3 (0 – 9)	NA	NA	3 (0 – 9)	3 (0 – 9)	NA	NA
Days from diagnosis to admission, median (range)	0 (0 – 4)	0 (0 – 3)	0 (0 – 4)	0.674	0 (0 – 4)	0 (0 – 3)	0 (0 – 4)	0.873
Underlying illness								
Diabetes	187 (36.9)	102 (39.8)	85 (33.9)	0.163	132 (38.4)	68 (39.5)	64 (37.2)	0.657
Hypertension	273 (53.8)	131 (51.2)	142 (56.6)	0.223	178 (51.7)	88 (51.2)	90 (52.3)	0.829
Coronary artery disease	46 (9.1)	27 (10.5)	19 (7.6)	0.243	33 (9.6)	17 (9.9)	16 (9.3)	0.855
Chronic lung disease	19 (3.7)	16 (6.3)	3 (1.2)	0.004	8 (2.3)	5 (2.9)	3 (1.7)	0.723
Chronic kidney disease	5 (1.0)	1 (0.4)	4 (1.6)	0.212	4 (1.2)	0 (0.0)	4 (2.3)	0.123
Malignancy	11 (2.2)	5 (2.0)	6 (2.4)	0.770	7 (2.0)	3 (1.7)	4 (2.3)	0.999
Immunocompromised	2 (0.4)	0 (0.0)	2 (0.8)	0.245	2 (0.6)	0 (0.0)	2 (1.2)	0.499
Liver cirrhosis	2 (0.4)	2 (0.8)	0 (0.0)	0.499	2 (0.6)	2 (1.2)	0 (0.0)	0.499
Cerebrovascular disease	35 (6.9)	18 (7.0)	17 (6.8)	0.909	27 (7.8)	13 (7.6)	14 (8.1)	0.999
COVID-19 vaccination	128 (25.2)	63 (24.6)	65 (25.9)	0.739	92 (26.7)	46 (26.7)	46 (26.7)	0.999
One dose	99 (19.5)	51 (19.9)	48 (19.1)	0.821	75 (21.8)	37 (21.5)	38 (22.1)	0.896
Two doses	29 (5.7)	12 (4.7)	17 (6.8)	0.312	17 (4.9)	9 (5.2)	8 (4.7)	0.804
Initial symptoms and sign								
Fever or chill	205 (40.4)	124 (48.4)	81 (32.3)	<0.001	144 (41.9)	72 (41.9)	72 (41.9)	0.999
Myalgia	110 (21.7)	70 (27.3)	40 (15.9)	0.002	76 (22.1)	40 (23.3)	36 (20.9)	0.603
Cough	270 (53.3)	151 (59.0)	119 (47.4)	0.009	180 (52.3)	91 (52.9)	89 (51.7)	0.829
Sputum	135 (26.6)	78 (30.5)	57 (22.7)	0.048	99 (28.8)	49 (28.5)	50 (29.1)	0.905
Dyspnea	19 (3.7)	15 (5.9)	4 (1.6)	0.017	6 (1.7)	3 (1.7)	3 (1.7)	0.999
Congestion or runny nose	53 (10.5)	26 (10.2)	27 (10.8)	0.825	35 (10.2)	20 (11.6)	15 (8.7)	0.373
Sore throat	144 (28.4)	76 (29.7)	68 (27.1)	0.517	90 (26.2)	45 (26.2)	45 (26.2)	0.999
Chest discomfort	18 (3.6)	8 (3.1)	10 (4.0)	0.601	14 (4.1)	7 (4.1)	7 (4.1)	0.999
Abdominal pain or diarrhea	21 (4.1)	10 (3.9)	11 (4.4)	0.788	12 (3.5)	7 (4.1)	5 (2.9)	0.770
Headache	114 (22.5)	70 (27.3)	44 (17.5)	0.008	79 (23.0)	40 (23.3)	39 (22.7)	0.898
Loss of taste or smell	33 (6.5)	14 (5.5)	19 (7.6)	0.338	25 (7.3)	11 (6.4)	14 (8.1)	0.533
Fever ≥38°C on admission	83 (16.4)	65 (25.4)	18 (7.2)	<0.001	43 (12.5)	25 (14.5)	18 (10.5)	0.254
Severity[b] on admission								
No symptom	34 (6.7)	9 (3.5)	25 (10.0)	0.004	21 (6.1)	9 (5.2)	12 (7.0)	0.499
Mild	236 (46.5)	88 (34.4)	148 (59.0)	<0.001	159 (46.2)	76 (44.2)	83 (48.3)	0.449
Moderate	237 (46.7)	159 (62.1)	78 (31.1)	<0.001	164 (47.7)	87 (50.6)	77 (44.8)	0.280
Laboratory findings on admission[c]								
WBCs (× 10^3/mm^3)	4.94 (4.08 – 6.04)	4.83 (4.05 – 5.87)	5.14 (4.11 – 6.23)	0.110	4.92 (4.11 – 5.90)	4.90 (4.10 – 5.80)	4.95 (4.11 – 5.93)	0.507
Platelet (× 10^3/mm^3)	199 (160 – 238)	197 (158 – 234)	202 (165 – 243)	0.195	200 (164 – 241)	200 (163 – 237)	198 (165 – 243)	0.673
AST (IU/L)	24 (19 – 31)	25 (20 – 32)	23 (19 – 31)	<0.001	24 (19 – 31)	24 (19 – 30)	24 (19 – 33)	0.909
ALT (IU/L)	19 (14 – 29)	19 (14 – 28)	19 (13 – 31)	0.185	18 (14 – 29)	18 (14 – 27)	19 (13 – 31)	0.758
Creatinine (mg/dL)	0.79 (0.65 – 0.94)	0.79 (0.65 – 0.94)	0.79 (0.66 – 0.94)	0.863	0.79 (0.65 – 0.95)	0.79 (0.65 – 0.95)	0.78 (0.65 – 0.95)	0.948
C-reactive protein (mg/dL)	0.47 (0.14 – 1.28)	0.63 (0.23 – 1.70)	0.29 (0.10 – 0.68)	<0.001	0.44 (0.14 – 1.28)	0.57 (0.19 – 1.48)	0.33 (0.12 – 0.93)	0.002
Outcomes								
Progress to severe disease	51 (10.1)	20 (7.8)	31 (12.4)	0.089	38 (11.0)	8 (4.7)	30 (17.4)	<0.001
Transfer to tertiary hospitals	6 (1.2)	3 (1.2)[d]	3 (1.2)[e]	0.999	4 (1.2)	1 (0.6)	3 (1.7)	0.311
Duration of hospitalization	11 (5 – 33)	11 (6 – 22)	11 (5 – 33)	0.010	11 (5 – 33)	11 (6 – 20)	11 (5 – 33)	0.329

Data are no. (%) of patients or median (interquartile range), unless otherwise indicated.
[a]Of the total cohort, 374 had COVID-19 symptoms at the time of admission.
[b]Severity was classified based on NIH-guidelines.
[c]Of the total cohort, 37 patients did not get laboratory tests.
[d]One patient was treated with high flow oxygen therapy and two were treated with low flow oxygen therapy in tertiary hospitals.
[e]Two patients were treated with high flow oxygen therapy and one was treated with mechanical ventilation.
COVID-19, coronavirus disease 2019; BMI, body mass index; NA, not applicable; WBC, white blood cell; AST, aspartate transaminase; ALT, alanine transaminase.

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RESULTS

1. Patient demographics

Of 2,236 adults admitted to MMC, 586 had at least one risk factor rendering monoclonal antibody treatment appropriate. In total, 507 patients were included in the analysis: a monoclonal antibody group (n = 256) and a control group (n = 251). Furthermore, 79 patients met the exclusion criteria (**Fig. 1**). The baseline characteristics of both groups are listed in **Table 1**. The median age was 66 years (interquartile range, 60 - 72 years) and 47.5% of the patients were men. The most common underlying illnesses were hypertension (53.8%), diabetes (36.9%), coronary artery disease (9.1%), cerebrovascular disease (6.9%), and chronic lung disease (3.7%). Patients were admitted to the hospital at a median of 2 days (range, 0 - 9 days) from symptom onset, indicating admission on the day of diagnosis (median, 0 days; range, 0 - 4 days). Regdanvimab was administered at a median of 3 days (range, 0 - 9 days) from symptom onset and at a median of 1 day (range, 0 - 7 days) from admission. Before matching (compared with controls), the treatment group exhibited more COVID-19 symptoms, more chronic lung disease, more temperatures >38°C on admission, and more cases of moderate COVID-19 on admission. Propensity score-matching yielded 172 patients in each group. The baseline characteristics were adequately balanced, as revealed by the standardized mean differences (**Supplementary Table 1** and **Fig. 1**).

2. Clinical outcomes

Progression to severe COVID-19 occurred in 20 (7.8%) monoclonal antibody-treated patients and 31 (12.4%) untreated patients ($P = 0.089$), including 3 of each pre-matched cohort who were transferred to university hospitals. There were no deaths. Although the duration of hospitalization slightly differed between the pre-matched groups, this difference

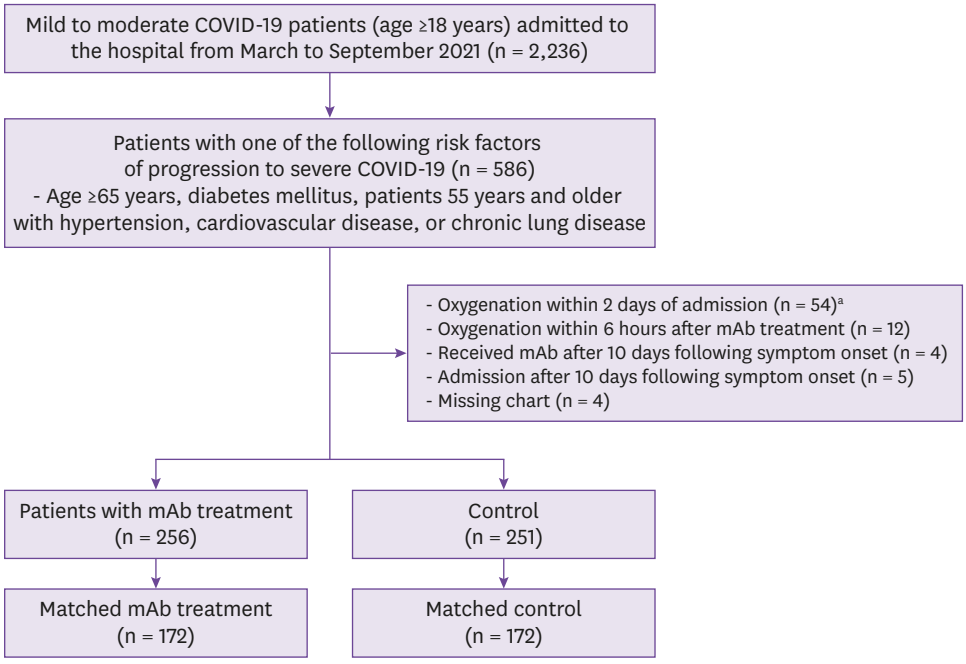

Figure 1. The study population.
[a]Of the 54 patients, 49 (90.7%) required oxygenation on the day of admission.
COVID-19, coronavirus disease 2019; mAb, monoclonal antibody.

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disappeared after propensity score-matching (P = 0.329) (**Table 1**). After adjustments for age, hypertension status, body temperature on admission, C-reactive protein (CRP) level, platelet count, COVID-19 vaccination status, and disease severity, regdanvimab was significantly associated with a reduced risk of disease progression during hospitalization [odds ratio (OR), 0.285; 95% confidence interval (CI), 0.144 - 0.564]. Hypertension, CRP level ≥1 mg/dL, platelet count <150 × 10^3/mm^3 and moderate disease severity on admission were significantly associated with disease progression (**Table 2**). In the propensity score-matched cohort, progression to severe COVID-19 occurred in 8 (4.7%) monoclonal antibody-treated patients and 30 (17.4%) untreated patients (P <0.001), including 1 and 3 patients (respectively) who were transferred to university hospitals (**Table 1**). After adjustments for hypertension, body temperature on admission, CRP level, platelet count, COVID-19 vaccination status, and disease severity, regdanvimab significantly reduced the risk of disease progression during hospitalization (OR: 0.162; 95% CI: 0.068 - 0.386) in the propensity score-matched cohort (**Table 2**). Kaplan–Meier survival analysis also revealed a significant difference in disease progression within 2 weeks after hospitalization between the two groups (log-rank test P <0.001; **Fig. 2B**).

Table 2. Association of baseline characteristics and regdanvimab treatment on disease progression in patients with COVID-19

Variables	Pre-matched cohort (n = 507)		Propensity score-matched cohort (n = 344)	
	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Age, ≥65 years	1.872 (0.970 – 3.611)	1.722 (0.840 – 3.532)	1.635 (0.746 – 3.583)	
Male	0.686 (0.380 – 1.239)		0.734 (0.369 – 1.460)	
Diabetes	1.116 (0.617 – 2.021)		1.708 (0.868 – 3.361)	
Hypertension	2.464 (1.297 – 4.681)	2.766 (1.388 – 5.509)	3.395 (1.555 – 7.412)	3.170 (1.379 – 7.286)
Coronary artery disease	0.839 (0.288 – 2.443)		0.789 (0.229 – 2.719)	
Chronic lung disease	0.487 (0.064 – 3.723)			
Cerebrovascular disease	1.167 (0.395 – 3.450)		1.007 (0.288 – 3.517)	
BMI ≥30 kg/m^2	0.890 (0.202 – 3.922)		1.833 (0.381 – 8.819)	
Fever ≥38°C on admission	2.654 (1.391 – 5.063)	1.929 (0.874 – 4.257)	2.955 (1.318 – 6.624)	2.144 (0.824 – 5.578)
C- reactive protein ≥1 mg/dL	3.977 (2.186 – 7.234)	3.572 (1.836 – 6.951)	3.655 (1.829 – 7.304)	3.950 (1.838 – 8.489)
WBCs >10 × 10^3/mm^3	1.030 (0.126 – 8.407)		1.926 (0.210 – 17.693)	
Platelet <150 × 10^3/mm^3	2.781 (1.466 – 5.275)	2.322 (1.141 – 4.727)	2.269 (1.049 – 4.905)	1.702 (0.688 – 4.214)
COVID-19 vaccination	1.014 (0.522 – 1.971)	0.673 (0.314 – 1.443)	1.132 (0.537 – 2.385)	0.753 (0.314 – 1.806)
Two doses of vaccination	0.649 (0.150 – 2.810)		1.078 (0.237 – 4.906)	
Moderate severity *vs.* No symptom to mild	3.045 (1.622 – 5.717)	3.049 (1.489 – 6.244)	2.310 (1.139 – 4.685)	2.167 (0.996 – 4.717)
Regdanvimab treatment	0.601 (0.333 – 1.086)	0.285 (0.144 – 0.564)	0.231 (0.103 – 0.520)	0.162 (0.068 – 0.386)

COVID-19, coronavirus disease 2019; OR, odds ratio; CI, confidence interval; BMI, body mass index; WBC, white blood cell.

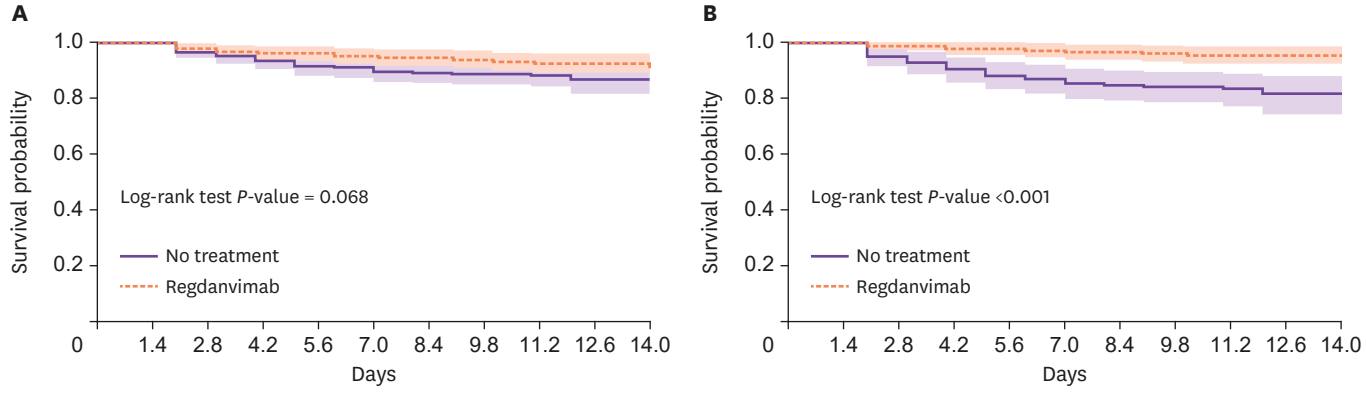

Figure 2. Kaplan–Meier curves of disease progression within 2 weeks of hospitalization.
The shaded area indicates the 95% confidence interval. (A) pre-matched cohort; (B) propensity score-matched cohort.

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We performed subgroup analyses before and after July 2021 (*i.e.*, divided by the Delta variant-dominant wave in Korea). Multivariate analyses of the pre-matched cohorts showed that the preventive effect of regdanvimab appeared to decrease after commencement of the Delta variant-dominant wave [OR: 0.100 (95% CI: 0.031 - 0.320) before the wave *vs.* OR, 0. 464 (95% CI: 0.183 - 1.175) after the wave]. The data from the propensity score-matched cohort showed a similar trend [OR: 0.032 (95% CI: 0.004 - 0.260) before the wave *vs.* OR: 0.414 (95% CI: 0.143 - 1.195) after the wave]. However, vaccination appeared to prevent disease progression after commencement of the Delta variant-dominant wave (OR: 0.414; 95% CI: 0.173 - 0.990) in the pre-matched cohort (**Supplementary Table 2**, **3**). We noted no serious adverse infusion-related events among regdanvimab-treated patients during the study period.

DISCUSSION

In this retrospective study, we found that regdanvimab treatment of mild-to-moderate COVID-19 was significantly associated with a decreased risk of progression to severe disease during hospitalization. It is difficult to compare the effect of regdanvimab to the effects of other neutralizing antibody therapies approved by the US FDA (*i.e.*, bamlanivimab–etesevimab, casirivimab–imdevimab, and sotrovimab) because of differences in the clinical settings and outcome measures. We included only patients who met the US FDA criteria for monoclonal antibody use. Our results are consistent with previous reports that monoclonal antibody treatment prevented mild-to-moderate COVID-19 from progressing to severe disease (*i.e.*, hospitalization) by 70.0 - 80.0% [17].

Unlike other monoclonal antibodies, limited data are available concerning regdanvimab. One Phase II trial reported that the proportions of patients requiring hospitalization or oxygen to day 28 were 4.0% and 4.9% in regdanvimab 40 and 80 mg/kg groups, but 8.7% in a placebo group. A preliminary Phase III trial found that regdanvimab reduced the risk of hospitalization or death with 28 days by 72% (compared to placebo) in high-risk patients with mild-to-moderate COVID-19 (P <0.01) [18]. We found that regdanvimab was useful for treating mild-to-moderate COVID-19 in a real-world setting.

In one randomized controlled trial, bamlanivimab was no better than standard therapy in hospitalized COVID-19 patients; the primary outcome was sustained recovery over a 90-day period [19]. Of 314 patients, 77.0% exhibited a disease status exceeding “severe” and monoclonal antibodies were administered at a median of 7 days from symptom onset. Based on this work and other clinical trials, the US guideline recommends monoclonal antibody treatment for ambulatory at-risk patients with mild-to-moderate COVID-19 [20]. Although our primary outcome was progression to severe COVID-19 in hospitalized patients with mild-to-moderate COVID-19, we acknowledge that it is difficult to directly compare our results with the results of previous studies that employed hospitalization or emergency room visits as primary outcomes [17].

As SARS-CoV-2 variants such as Delta and Omicron, there has been increasing concern that monoclonal antibody effects will decrease. An *in vitro* study showed that bamlanivimab was not active against the Delta variant, while etesevimab, casirivimab, and imdevimab remained active [21]. *In vitro* and in a mouse model, regdanvimab was active against Delta, but showed less activity than it did against Delta precursors [22]. However, we found that the preventive effect of regdanvimab appeared to decrease during the Delta variant-dominant wave.

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Importantly, it is difficult to draw firm conclusions because more patients became vaccinated and there were a relatively small number of cases during the Delta variant-dominant wave. Furthermore, we do not know the proportions of Delta-infected cases; genomic sequencing data were lacking. According to the Korea Disease Control and Prevention Agency, >50.0% of random samples collected in mid-July and >90.0% collected in early August were Delta. It may thus be possible to compare the effect of regdanvimab before and after the Delta variant-dominant wave in this study. Omicron is rapidly outpacing Delta globally and is driving an upsurge of infections in most regions [23]. *In vitro* data suggest that several monoclonal antibodies, including regdanvimab, lost neutralizing activity against Omicron [24]. Although some monoclonal antibodies in clinical use may retain benefit, the use of monoclonal antibody therapeutics will require caution depending on whether Omicron is dominant in a region [25].

Our work had several limitations. First, although propensity score-matching was used to reduce selection bias and confounding, many cases were discarded during this process, possibly creating (rather than eliminating) selection bias. However, multiple logistic regression analysis yielded similar results. Second, we excluded patients who progressed to severe or critical status within 2 days of hospitalization or within 6 h of regdanvimab administration. Because progression to severe or critical COVID-19 disease usually occurred soon after hospitalization, such patients were less likely to receive regdanvimab; this may have exaggerated the effect of the drug. We excluded such patients to render our analysis conservative. Third, neither the duration of hospitalization nor the time to symptom improvement served as a principal outcome, because patients were discharged only when they met the government guideline regardless of whether they had recovered earlier. Finally, minor symptoms might not have been recorded by attending physicians or nurses.

In conclusion, our real-world study suggests that regdanvimab treatment of mild-to-moderate COVID-19 significantly reduced disease progression; the effect appeared to wane during the Delta variant-dominant wave. A large-scale prospective study or randomized clinical trial is needed to explore the effects of regdanvimab in the era of Omicron domination and high numbers of vaccinated individuals.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1

Standardized mean differences before and after propensity score matching

Click here to view

Supplementary Table 2

Association of clinical characteristics and disease progression in the pre-matched cohort with COVID-19 before and after the Delta variant-dominant wave in Korea

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Supplementary Table 3

Association of clinical characteristics and disease progression in the propensity score-matched cohort with COVID-19 before and after the Delta variant-dominant wave in Korea

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Supplementary Figure 1

Visualization of the distribution of propensity score by the jitter plot.

Click here to view

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