Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Regdanvimab improves disease mortality and morbidity in patients with COVID-19: A meta-analysis

Dear editor,

We read with great interest that biologic medications might be a promising therapeutic option in COVID-19.[1] Neutralizing monoclonal antibodies such as regdanvimab can reduce virulence, viral load, and improve outcomes through passive immunotherapy, making them an attractive option for treatment of COVID-19 infection.[2]

Regdanvimab was developed for the treatment of COVID-19 and first received full approval in South Korea in September 2021 for use in patients over the age of 50 with mild COVID-19 symptoms and at least one of several defined underlying conditions or in adults with moderate symptoms.[3] At the time of writing, regdanvimab has also been approved for use in Europe for at-risk adults who do not require supplemental oxygen therapy and for emergency use in Indonesia and Brazil with steps towards approval in Canada and the United States.[3] By strongly binding to the receptor binding domain of the spike protein of SARS-CoV-2, regdanvimab inhibits viral internalization through steric hinderance with the ACE2 receptor.[2] Importantly, regdanvimab also effectively neutralizes the D614G mutation, which is present in the Omicron variant and is associated with higher viral load and transmissibility.[2]

There have been no prior meta-analyses describing the association between the usage of regdanvimab and patient prognosis following COVID-19 infection to the best of our knowledge. We perform in this study the first meta-analysis in the literature to evaluate the relationship between regdanvimab administration and patient outcomes following COVID-19 infection.

An extensive electronic search was conducted in PubMed, Embase, Cochrane Library databases, Scopus and medRxiv) from December 1 2019 to April 23th, 2022. The search was performed without any restrictions on language or publication type. The following medical subject heading terms (MeSH) and key words were included for databases search as needed: ("or coronavirus disease 2019 or novel coronavirus or 2019-nCoV or COVID-19 or SARS-CoV-2") AND (regdanvimab or CT-P59).

The inclusion criteria were defined as follows: (1) PCR-confirmed cases of COVID-19; (2) reports containing original data with available risk estimates and/or with data on the number of deaths in regdanvimab and control groups; and (3) comparative studies with a control group with no regdanvimab. Following studies were excluded (1) reviews, conference abstracts, editorials, letters, and case reports; and (2) duplicated publications. The following details were extracted from eligible studies: first author's name, year of publication, location of participants, research design, number of participants, age, gender, usage of regdanvimab, outcomes of interest (mortality and composite outcome).

The statistical analysis was conducted using Review Manager, version 5.2 (Cochrane Collaboration, Oxford). Odds ratio (OR) and its 95% confidence interval (CI) were used to analyze the dichotomous variables. Heterogeneity was assessed by the Cochrane Q test and I^2 test. A p value of less than 0.05 was considered to show a statistically significant result. This meta-analysis is registered with PROSPERO (International Prospective Register of Systematic Reviews, No. CRD42022328533).

The electronic search identified a total of 7 studies,[2,4–9] one of which were randomized controlled trials and the others were retrospective studies. This meta-analysis included 1350 patients in the regdanvimab group, 1983 patients in the control group. Demographics and disease characteristics of the 3333 patients included in the pooled analysis are summarized in Table 1. The seven studies were published between 2021 and 2022 with different sample patient sizes that ranged from 152 to 897 patients with COVID-19. All included studies were conducted in Korea and carried out on hospitalized mild-to-moderate COVID-19 patients except for one.[4] Regdanvimab was intravenously administered in the included studies. Composite outcome included need for supplemental oxygen and/or progression to severe disease.

The meta-analysis showed the overall mortality was lower in the regdanvimab group compared to control group (OR = 0.14, 95%CI: 0.03 to 0.56, P = 0.006; I^2 = 0%) (Fig. 1A). Moreover, regdanvimab treatment was associated with reduced risk of the composite outcome (OR = 0.35, 95%CI: 0.19 to 0.65, P = 0.001; I^2 = 74%) (Fig. 1B) compared with control group.

In this study, we find that the use of regdanvimab to treat patients with COVID-19 is associated with a significant benefit in overall mortality as well as our composite endpoint, suggesting improvements in morbidity as well.

While these findings are positive, there are specific indications for use of regdanvimab. It has only been approved for usage in patients with mild or moderate level of illness, a patient population that has an inherently better disease prognosis than severe infections. COVID-19 also continues to evolve and increase pressures on healthcare systems, with previously effective treatment options losing their impact as a result of mutations in the SARS-CoV-2 genome. In particular, growing concerns with the omicron variant and its XE subvariant have raised questions regarding diminishing susceptibilities to therapeutic approaches.[10] Emerging in vitro data has also suggested that the omicron variant has developed resistance to the neutralizing effect of therapeutic monoclonal antibodies, including regdanvimab.[10] This finding is especially pertinent as five of the seven included studies did not collect data on the variants of concern in their study participants, three of which assumed most of the patients in their study had wild-type. The remaining two included studies suggested efficacy against the delta variant, however, further investigation is needed regarding efficacy in more recent variants of concern.

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Table 1
Characteristics of included studies.

Study	Region	Regdanvimab		Control		Study design	Sample size	Patients included	Usage of regdanvimab
		Age[a]	Male (%)	Age[a]	Male (%)				
Choi[2] 2022	Korea	66 (57–75)	29 (44.6)	60 (48–68)	149 (44.7)	Retrospective cohort study	398	Hospitalized mild-to-moderate COVID-19	NR
Cercel[4] 2022	Asia, Europe, USA	51.0 (40–60)	118 (54.6)	52.0 (41–61)	48 (43.2)	RCT	327	Outpatients with mild-to-moderate COVID-19	A single dose of regdanvimab 40 mg/kg or 80 mg/kg
Hong[5] 2022	Korea	66 (60–72)	122 (47.7)	67 (60–72)	119 (47.4)	Retrospective observational study	507	Hospitalized mild-to-moderate COVID-19	A single intravenous infusion of 40 mg/kg
JY Lee[6] 2021	Korea	51.8 ± 14.3	130 (55.6)	56.2 ± 15.3	267 (49.1)	Retrospective cohort study	778	Hospitalized mild-to-moderate COVID-19	Intravenously with the dose of 40 mg/kg
Kim[7] 2022	Korea	46.9 (43.9–49.8)	44 (49.4)	36.1 (32.9–39.3)	33 (52.4)	Retrospective observational study	152	Hospitalized mild-to-moderate COVID-19	A single intravenous infusion of 40 mg/kg
Park[8] 2022	Korea	61 (53–68)	164 (44.4)	65 (57–75)	205 (55.6)	Retrospective cohort study	897	Hospitalized mild-to-moderate COVID-19	A single intravenous infusion of 40 mg/kg
S Lee[9] 2022	Korea	64.0 (26–90)	72 (63.7)	63.0 (25–97)	86 (53.4)	Retrospective observational study	274	Hospitalized mild-to-moderate COVID-19	40 mg/kg as an intravenous infusion

[a] Age data presented as median (IQR) or mean (SD); RCT: randomized controlled trial; NR: not reported.

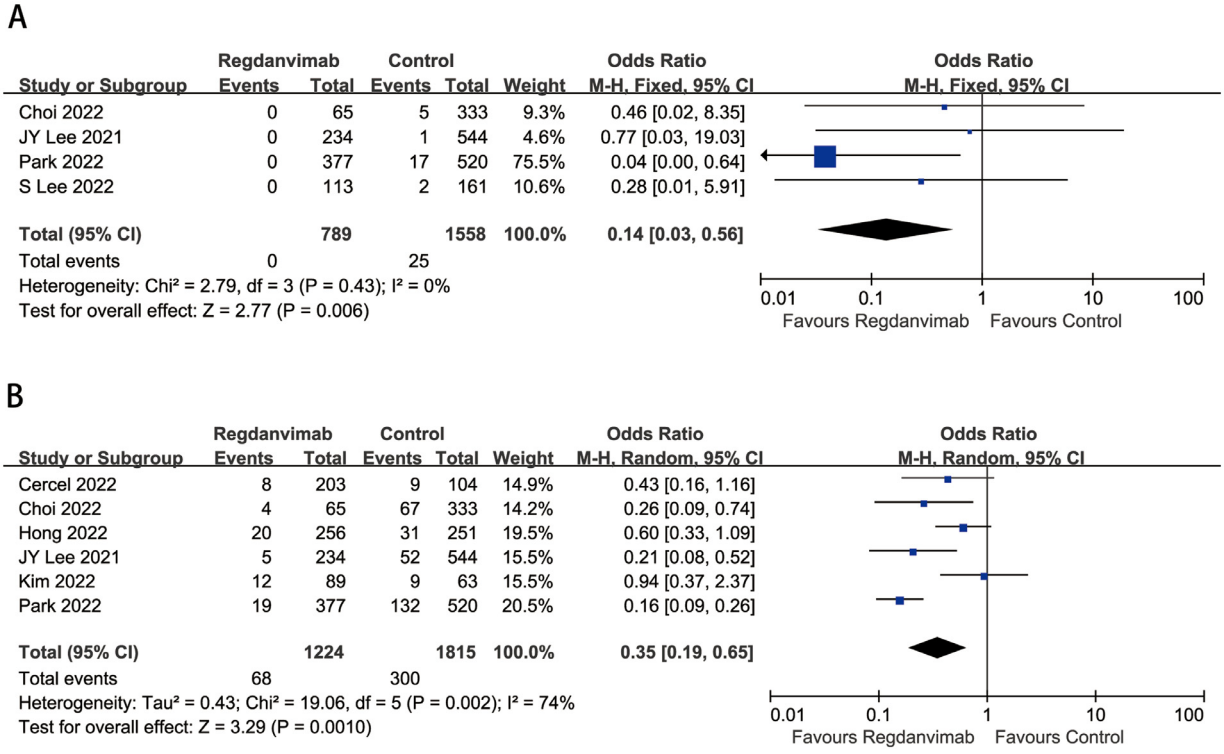

Fig. 1. A Association between regdanvimab treatment and mortality. B Association between regdanvimab treatment and composite outcome.

Whether there is a synergistic effect between regdanvimab treatment and COVID-19 vaccination remains to be elucidated. Only one of the seven included articles excluded vaccinated patients, while the remaining studies had wide variance in the vaccination status and efficacy of their participants. The study period of one earlier article occurred prior to widespread vaccine distribution and thus a small minority of their participants were vaccinated, while another more recent study found no breakthrough infections after vaccination in their participants. With newer variants and subvariants exhibiting increasing immune escape properties, there continues to be considerable value in identifying novel therapeutic approaches.[10]

There are several limitations with our study that should be noted. The meta-analysis had a relatively small sample size for

use with seven included studies, of which only four had mortality data for analysis. In addition, while there were no heterogeneity concerns with the mortality analysis, the composite end point results had significant heterogeneity ($I^2 > 50\%$), likely secondary to having a combination of component endpoints. Furthermore, all but one of our included studies consisted of patient populations solely from South Korea. Despite these limitations, our study is the first meta-analysis to investigate the association between treatment with regdanvimab and COVID-19 infection associated morbidity and mortality.

Additional investigation is needed to explore the impact of regdanvimab treatment on patient outcomes following COVID-19 infection to provide additional insight and better understand the factors contributing to its efficacy, including patient populations of other geographic regions, varying severities of COVID-19 infection, and in different variants of concern.

In conclusion, treatment with regdanvimab in patients with COVID-19 infection is associated with significant benefit in both mortality rate and our composite endpoint. Further research is required to corroborate these findings.

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Declaration of Competing Interest

The authors declare that they have no competing interest.

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