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Use of Darunavir-Cobicistat as a Treatment Option for Critically Ill Patients with SARS-CoV-2 Infection

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We retrospectively reviewed patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections who were admitted to an intensive care unit in Daegu, South Korea. The outcomes of patients who did (cases) or did not (controls) receive darunavir-cobicistat (800–150 mg) therapy were compared. Fourteen patients received darunavir-cobicistat treatment, and 96 received other antiviral therapy (controls). Overall, the darunavir-cobicistat group comprised patients with milder illness, and the crude mortality rate of all patients in the darunavir-cobicistat group was lower than that in the controls [odds ratio (OR) 0.20, 95% confidence interval (CI) 0.04–0.89, p=0.035]. After 1:2 propensity-score matching, there were 14 patients in the darunavir-cobicistat group, and 28 patients in the controls. In propensity score-matched analysis, the darunavir-cobicistat group had lower mortality than the controls (OR 0.07, 95% CI 0.01–0.52, p=0.009). In conclusion, darunavir-cobicistat therapy was found to be associated with a significant survival benefit in critically ill patients with SARS-CoV-2 infection.

Key Words: Coronavirus disease 2019, severe acute respiratory syndrome coronavirus 2, darunavir-cobicistat

On March 11, 2020, the World Health Organization (WHO) declared the coronavirus disease 2019 (COVID-19) a pandemic. Until May 20, 2020, there were more than 4.9 million reported COVID-19 cases and 324869 deaths across more than 200 countries. Currently, there are no specific therapeutic agents for treating severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Potential drugs for treating COVID-19 include human immunodeficiency virus (HIV) type 1 aspartate protease inhibitors, such as lopinavir and darunavir, which have been shown to inhibit SARS-CoV in vitro, the cause of SARS in humans.[1-4] Cobicistat-boosted darunavir is a boosted protease inhibitor in a fixed-dose combination that is approved for use in treating HIV type 1 infection.[5,6] Drug efficacy evaluation in cell models in vitro have revealed that darunavir is active against SARS-CoV-2.[2] At present, however, there are no clinical data on the use of these drugs for COVID-19.

Cobicistat-boosted darunavir is stable as a suspension,[7] so it was considered to be suitable for administration as a nasogastric tube to critical ill patients. Here, we evaluated the effects of darunavir-cobicistat on the clinical outcomes of critically ill patients with COVID-19 using a risk stratification model that adjusted for potential differences between the darunavir-cobicistat treated and non-darunavir-cobicistat treated individuals.

We retrospectively reviewed the medical records of all adults with laboratory-confirmed SARS-CoV-2 infection who were subsequently admitted to an intensive care unit (ICU) at one of the

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seven tertiary or referral hospitals in Daegu, South Korea between February 18 and April 5, 2020. A WHO guidance document defines laboratory confirmation of SARS-CoV-2 infection as a positive result of a real-time reverse transcriptase-polymerase chain reaction assay of samples obtained from nasal and pharyngeal swabs. The first part of this study was a retrospective cohort study that included all patients who were critically ill with laboratory-confirmed SARS-CoV-2 infection. Cobicistat-boosted darunavir was assigned to patients who failed other antiviral treatments or at the physician's discretion. The outcomes of patients who did (cases) or did not (controls) receive darunavir-cobicistat (800–150 mg) therapy were compared. The second part of the investigation comprised a matched (1:2) case-control study, with the patients who did or did not receive darunavir-cobicistat therapy designated as "cases" and "controls" (Fig. 1), respectively. This study was conducted in accordance with the tenets of the Declaration of Helsinki and was reviewed and approved by the Institutional Review Board at each hospital. The requirement for informed consent was waived because of the retrospective study design (IRB Number: YUH IRB 2020-03-057, IRB Institution: Yeungnam University Medical Center).

The present study included 110 critically ill patients who received intensive care for COVID-19, of whom 14 received darunavir-cobicistat treatment and 96 received other antiviral therapy.

There were no significant intergroup differences with regard to age, sex ratio, body mass index, and underlying disease/conditions between the groups who did and did not receive darunavir-cobicistat treatment (Table 1). Sequential Organ Failure Assessment (SOFA) scores {median score 2 [interquartile range (IQR) 2–4] vs. 6 [IQR 3–8], $p<0.001$} and National Early Warning Scores [median score 6 (IQR 5–7) vs. 8 (IQR 5–11), $p<0.001$] were significantly lower in the darunavir-cobicistat group than in the controls, indicating that the darunavir-cobicistat group had patients with milder illness. The incidence of shock and acute respiratory distress syndrome (ARDS) during hospitalization did not differ between the two groups. There were no between-group differences in the length of ICU stay or survival, although the number of deaths was significantly lower in the darunavir-cobicistat treatment group (14.3% vs. 46.9%, $p=0.021$). There were also significant differences in the numbers of patients who survived and were discharged from the ICU: 10 (83.3%) in the darunavir-cobicistat group and 29 (39.2%) in the controls ($p=0.004$). The crude mortality rates of all patients and ARDS patients in the darunavir-cobicistat group were lower than those in the controls [odds ratio (OR) 0.20, 95% confidence interval (CI) 0.04–0.89, $p=0.035$ and OR 0.17, 95% CI 0.04–0.79, $p=0.024$, respectively) (Table 2). Mortality rates after adjusting for variables, such as age ≥65 years and SOFA score, were the same in both groups. Two variables, age ≥65 years and SOFA score, were selected for propensity-score matching based on outcomes of the univariate and multivariate analyses. After 1:2 propensity-score matching, there were 14 patients in the darunavir-cobicistat group and 28 in the controls. Table 1 shows the patient characteristics for both groups after matching the propensity scores; the two groups were balanced. The number of deaths was significantly lower in the darunavir-cobicistat group (14.3% vs. 50.0%, $p=0.025$). In the propensity score-matched analysis, the darunavir-cobicistat group had lower mortality than the controls (OR 0.09, 95% CI 0.01–0.52, $p=0.009$) (Table 2). Furthermore, the darunavir-cobicistat group, which comprised ARDS patients, had lower mortality than the controls (OR 0.08, 95% CI 0.01–0.50, $p=0.008$). To determine the effect of darunavir-cobicistat on COVID-19,

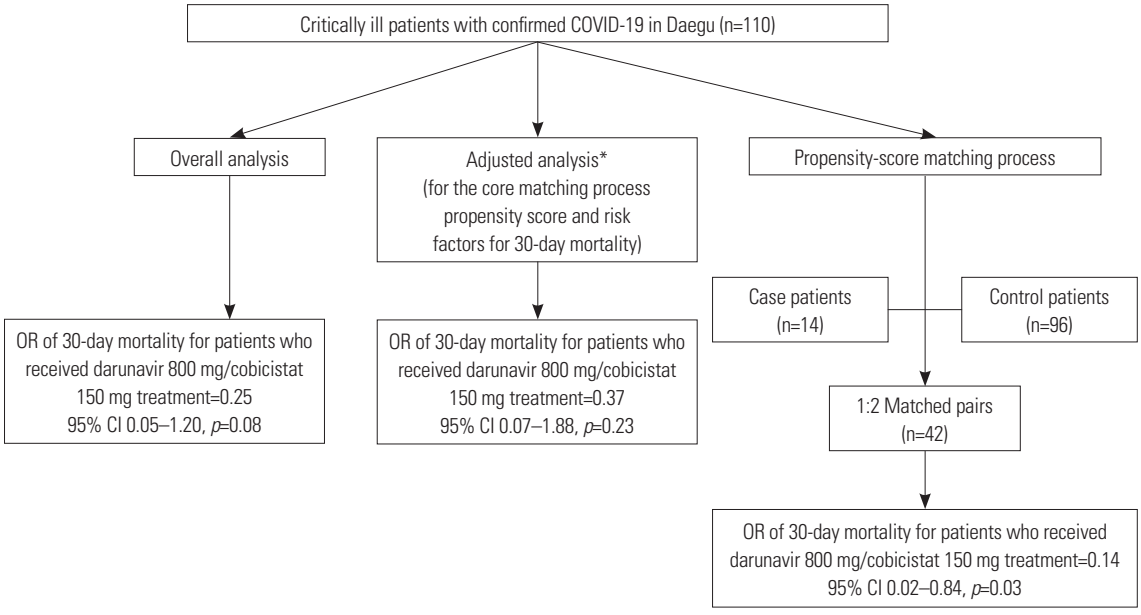

Fig. 1. Schematic representation of the data analysis plan for the cohort study and the matched case-control study. *Adjusted aged ≥65 years, Sequential Organ Failure Assessment. OR, odds ratio; CI, confidence interval.

Table 1. Baseline Demographics and Clinical Characteristics (n=110) of the Study Population

	DRV-COBI treatment (n=14)	No DRV-COBI treatment			
		Before matching (n=96)	*p* value*	After matching (n=28)	*p* value†
Median age (yr)	71 (64–74)	71 (63–78)	0.931	67 (62–76)	0.628
Age ≥65 years	11 (78.6)	65 (67.7)	0.543	17 (60.7)	0.313
Male sex	6 (42.9)	37 (38.5)	0.757	10 (35.7)	0.653
Body mass index	24.7 (22.0–26.6)	25.0 (22.0–27.1)	0.960	25.1 (22.2–27.1)	0.903
Underlying diseases/conditions					
Hypertension	8 (57.1)	47 (49.0)	0.567	9 (32.1)	0.120
Diabetes mellitus	5 (35.7)	35 (36.5)	0.957	7 (25.0)	0.491
Cardiovascular disease	1 (7.1)	8 (8.3)	>0.99	5 (17.9)	0.645
Chronic lung disease	1 (7.1)	8 (8.3)	>0.99	3 (10.7)	>0.999
Chronic renal disease	NA	11 (11.5)		3 (10.7)	
Chronic liver disease	1 (7.1)	4 (4.2)	0.501	1 (3.6)	>0.999
Malignancy	2 (14.3)	8 (8.3)	0.613	2 (14.3)	0.590
Connective tissue disease	NA	NA		NA	
No underlying diseases	10 (71.4)	69 (71.9)	>0.99	17 (60.7)	0.495
Severity of illness at admission					
APACHE II score	12 (7–14)	12 (7–14)	0.063	10 (7–14)	0.635
SOFA score	2 (2–4)	6 (3–8)	<0.001	3 (2–5)	0.284
NEWS	6 (5–7)	8 (5–11)	<0.001	6 (5–8)	0.711
CURB-65	2 (1–2)	2 (1–3)	0.361	1 (0–2)	0.203
Sign at admission					
Temperature, °C	37.5 (37.2–38.0)	37.0 (36.5–38.1)	0.385	37.3 (36.7–38.1)	0.609
Heart rate, beats/min	78 (69–82)	88 (76–102)	0.013	88 (81–94)	0.018
Systolic blood pressure, mm Hg	125 (113–140)	130 (110–148)	0.775	138 (120–148)	0.273
Mean arterial pressure, mm Hg	88 (81–97)	83 (83–107)	0.351	97 (88–109)	0.070
Leukocytes, cells/mm^3	5870 (4320–9715)	7190 (5173–11340)	0.229	6580 (4950–9090)	0.626
Lymphocytes, cells/mm^3	1190 (630–1990)	1060 (660–1940)	0.739	1150 (813–1795)	>0.999
Haemoglobin, g/dL	13.3 (12.3–14.5)	12.6 (10.6–14.0)	0.120	12.8 (11.4–13.6)	0.149
Platelets, cells/mm^3	239000 (158000–298000)	169500 (128500–235750)	0.101	165500 (127500–253250)	0.303
Creatinine, mg/dL	0.82 (0.69–1.11)	1.0 (0.7–1.4)	0.168	0.95 (0.69–1.17)	0.252
PaO_2 /FIO_2, mm Hg	180 (89–251)	129 (79–195)	0.213	151 (98–262)	0.836
Glucose, mg/dL	150 (114–179)	150 (117–197)	0.598	150 (129–173)	0.706
C-reactive protein, mg/dL	11.9 (5.0–19.6)	10.2 (6.0–15.2)	0.580	9.4 (6.0–16.0)	0.546
Sodium, mmol/L	137 (132–140)	136 (133–139)	0.689	134 (132–138)	0.857
Potassium, mmol/L	4.0 (3.6–4.7)	4 (3.5–4.6)	0.814	4.0 (3.4–4.5)	0.767
Shock	9 (64.3)	62 (64.6)	>0.99	19 (67.9)	>0.999
Acute respiratory distress syndrome	13 (92.9)	84 (87.5)	>0.99	26 (92.9)	>0.999
Treatment during study period					
Vasopressors	9 (64.3)	66 (68.8)	0.764	19 (67.9)	>0.999
Mechanical ventilation	10 (71.4)	69 (71.9)	>0.99	20 (71.4)	>0.999
High-flow nasal cannula	9 (64.3)	49 (51.0)	0.354	15 (63.6)	0.508
Renal replacement therapy	2 (14.3)	19 (19.8)	>0.99	3 (10.7)	>0.999
ECMO use	2 (14.3)	17 (17.7)	>0.99	2 (7.1)	0.590
Adjuvant corticosteroid use	8 (57.1)	80 (80.3)	0.033	22 (78.6)	0.169
Lopinavir-ritonavir	8 (57.1)	88 (91.7)	0.002	24 (85.7)	0.059
Hydroxychloroquine	13 (92.9)	86 (89.6)	>0.99	25 (89.3)	>0.999
Length of DRV/COBI treatment	6 (4–8)	NA		NA	
Length of ICU stay, days	13 (7–40)	15 (5–32)	0.618	13 (4–23)	0.320
Death	2 (14.3)	45 (46.9)	0.021	14 (50.0)	0.025

DRV-COBI, darunavir-cobicistat; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; NEWS, National Early Warning Scores; PaO_2, Partial pressure of oxygen in the arterial blood; FiO_2, percentage of inspired oxygen; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; NA, not applicable.
Data are presented as a median (interquartile range) or n%.
*p value of DRV-COBI treatment vs. no DRV-COBI treatment, before matching, †p value of DRV-COBI treatment vs. no DRV-COBI treatment, after matching.

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Table 2. Adjusted Effects of Mortality

	Crude		Adjusted mortality		Propensity-matched	
	OR (95% CI)	*p* value	Adjusted OR*	*p* value	Adjusted OR*	*p* value
All patients	0.20 (0.04–0.89)	0.035	0.32 (0.06–1.62)	0.169	0.07 (0.01–0.52)	0.009
Subgroup, ARDS	0.17 (0.04–0.79)	0.024	0.22 (0.04–1.10)	0.065	0.08 (0.01–0.50)	0.008

ARDS, acute respiratory distress syndrome; CI, confidence interval; OR, odds ratio.
*Adjusted aged ≥65 years, Sequential Organ Failure Assessment score.

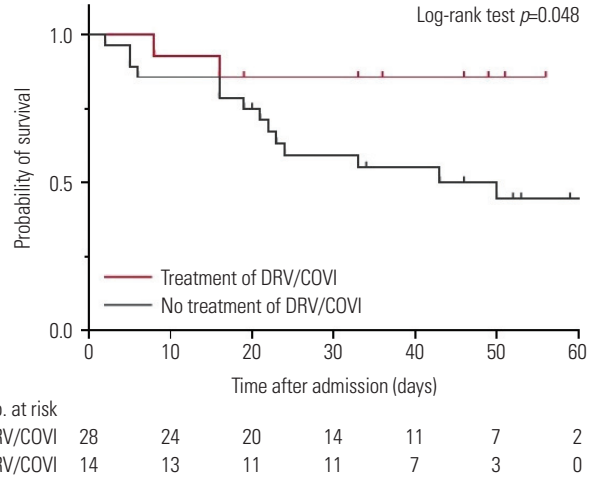

Fig. 2. Kaplan-Meier analysis for survival outcomes with darunavir-cobicistat (DRV-COVI) therapy plotted against time after admission with *p* values by log-rank test.

we subjected the matched cohorts to Kaplan-Meier analysis and noted a significant between-group difference in in-hospital survival rate (p=0.048, respectively) (Fig. 2).

To our knowledge, this is the first report to evaluate the treatment effect of darunavir-cobicistat in critically ill COVID-19 patients in whom darunavir-cobicistat therapy was associated with a significant survival benefit over standard treatment.

The mechanism of action underlying the effect of darunavir-cobicistat on SARS-CoV-2 remains to be elucidated. Several studies have evaluated the therapeutic effects of antiretroviral drugs in COVID-19, although the results are controversial. A recent randomised clinical trial by Cao, et al.[8] investigated the efficacy of lopinavir-ritonavir (400–100 mg, twice daily for 14 days) treatment in COVID-19 and showed no beneficial effect thereof over standard care in hospitalised adults with severe COVID-19. Regarding antiviral therapy with darunavir-cobicistat, there are no human clinical data on the use of this drug combination in COVID-19 patients, although a randomised clinical trial of darunavir-cobicistat is ongoing in China (NCT04252274).

This study has several limitations. First, because the study was retrospective, the possibility of selection bias cannot be excluded. Second, the propensity score matching method is limited because it adjusted only for observed covariates. Finally, there was a selection bias of using cobicistat-boosted darunavir only in 14 patients with physician preference and interference with other antiviral agents. Owing to this limitation, the conclusions of nonrandomised studies that use propensity scores must be assessed for consistency with other results, as well as for biological plausibility. Therefore, we suggest that preclinical studies and prospective clinical studies are needed to confirm these preliminary results.

In conclusion, darunavir-cobicistat therapy was associated with a significant survival benefit in critically ill patients with SARS-CoV-2 infection in this study. Further study of darunavir-cobicistat in relation to this highly virulent disease is needed.

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AUTHOR CONTRIBUTIONS

Conceptualization: Eun Young Choi. Data curation: all authors. Formal analysis: Eun Jin Kim and Sun Ha Choi. Funding acquisition: Eun Young Choi. Investigation: all authors. Methodology: Eun Jin Kim, Sun Ha Choi, and Eun Young Choi. Software: Eun Jin Kim, Sun Ha Choi, and Eun Young Choi. Validation: Eun Jin Kim, Sun Ha Choi, and Eun Young Choi. Writing—original draft: Eun Jin Kim, Sun Ha Choi, and Eun Young Choi. Writing—review & editing: Sun Ha Choi and Eun Young Choi. Approval of final manuscript: all authors.

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