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

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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 324,869 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
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 treatment 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 \( \geq 65 \) years and SOFA score, were the same in both groups. Two variables, age \( \geq 65 \) 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,

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**Fig. 1.** Schematic representation of the data analysis plan for the cohort study and the matched case-control study. *Adjusted aged \( \geq 65 \) 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 | 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 (36.5)             | 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/mm³   | 5870 (4320–9715)          | 7190 (5173–11340)     | 0.229     | 6580 (4950–9090)       | 0.626     |
| Lymphocytes, cells/mm³  | 1190 (630–1990)           | 1060 (660–1490)       | 0.739     | 1150 (613–1795)        | >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/mm³    | 239000 (158000–298000)    | 169500 (128500–235750) | 0.101     | 165500 (127500–252520) | 0.303     |
| Creatinine, mg/dL       | 0.82 (0.69–1.11)          | 1.0 (0.7–1.4)         | 0.188     | 0.95 (0.69–1.17)       | 0.252     |
| PaO₂/FiO₂, mm Hg        | 180 (69–251)              | 129 (79–195)          | 0.213     | 151 (88–262)           | 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 (5.0–18.6)          | 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 (3.4–4.7)             | 4.3 (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; PaO₂, Partial pressure of oxygen in the arterial blood; FiO₂, 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.
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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