Antiviral Activity and Safety of Darunavir/Cobicistat for the Treatment of COVID-19

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Background. We aimed to evaluate the antiviral activity and safety of darunavir/cobicistat (DRV/c) in treating COVID-19 patients.

Methods. In this single-center, randomized, and open-label trial, mild patients with polymerase chain reaction (PCR)–confirmed COVID-19 were enrolled in Shanghai, China. Participants were randomized to receive DRV/c for 5 days on the top of interferon alpha 2b inhaling or interferon alpha 2b inhaling alone. The primary end point was the virological clearance rate of oropharyngeal swabs at day 7 after randomization in the intention-to-treat population (clinicaltrials.gov: NCT04252274).

Results. From January 30, 2020, to February 6, 2020, a total of 30 patients were enrolled, of whom 18 (60%) were male, aged 47.2 ± 2.8 years; 63.3% (19/30) of the participants had fever, and 46.7% (14/30) had cough at enrollment. The participants were randomized (range) at 4 (2–5) days after onset of symptoms. The proportion of negative PCR results at day 7 was 46.7% (7/15) and 60.0% (9/15) in the DRV/c and control groups (P = .72), respectively. The viral clearance rate at day 3 was 20% (3/15) in both study groups, while the number increased to 26.7% (4/15) in the DRV/c group and remained 20% (3/15) in the control group at day 5. Fourteen days after randomization, 1 participant in the DRV/c group progressed to critical illness and discontinued DRV/c, while all the patients in the control group were stable (P = 1.0). The frequencies of adverse events in the 2 groups were comparable.

Conclusions. Five days of DRV/c did not increase the proportion of negative conversion vs standard of care alone, although it was well tolerated.

Keywords. antiviral activity; COVID-19; darunavir; protease inhibitors; SARS-CoV-2.
of DRV/c in treating pneumonia caused by the SARS-CoV-2. SPHCC is the only hospital in Shanghai to treat adult COVID-19 cases. The study aimed to enroll 30 participants, with a 1:1 randomization ratio (N = 15 subjects in each arm). All the participants had laboratory-confirmed SARS-CoV-2 infection and were willing to participate in the study, as evidenced by signing an informed consent. Participants were excluded if they met any of the following criteria: hypersensitivity to darunavir, cobicistat, or any excipients; patients with severe liver injury (Child-Pugh Class C); patients receiving concomitant medications that are highly dependent on cytochrome P450 3A clearance, and for which the elevated plasma concentrations are associated with serious or life-threatening events; subjects considered to be unable to complete the study (eg, severely and critically ill patients) or not suitable for the study by researchers. Patients who met any of the following criteria were classified as severe cases: respiratory rate ≥30 times/min, pulse oxygen saturation ≤93% at resting, or ratio between partial pressure of oxygen in arterial blood and fraction of inspired oxygen (PaO2/FiO2) ≤300 mmHg. Critical illness was defined as respiratory failure that needed mechanical ventilation or shock or exacerbation of any comorbidity that required transfer to the intensive care unit. This study was approved by the Ethics Committee of SPHCC, and informed consent was obtained from patients. The study is registered at ClinicalTrials.gov (NCT04252274).

Procedure
After informed consent, participants were randomized to the DRV/c group or the control group depending on the parity of their medical record number. All the participants received interferon alpha 2b and standard of care as per guideline recommendation in China [11]. Herein, participants in experiment group received 1 pill of DRV/c (a single-tablet regimen containing 800 mg of darunavir and 150 mg of cobicistat) per day for 5 days, while participants in the control group did not receive oral antiviral drugs.

Laboratory confirmation of SARS-CoV-2 was achieved by the Chinese Center for Disease Prevention and Control (CDC). Subsequent test of oropharyngeal swabs for SARS-CoV-2 after admission was performed by both SPHCC and CDC based on the recommendation of the National Institute for Viral Disease Control and Prevention (China), as previously described [12].

End Points
The primary end point was viral clearance rate at day 7 after randomization. After randomization, respiratory samples were collected every 1–2 days until viral clearance. Viral clearance was defined as reverse transcriptase polymerase chain reaction (RT-PCR) negative on at least 2 consecutive oropharyngeal swabs collected at least 1–2 days apart. Secondary end points included viral clearance at day 3 and day 5, the critical illness rate of subjects during the 14 days after randomization, the mortality rate of subjects at day 14, and the number of participants with treatment-related adverse events.

Statistical Analysis
Depending on the distribution of the data, categorical variables were described as frequency rates and percentages, and continuous variables were described with mean, median, and interquartile range (IQR) values. For the primary end point, both intention-to-treat (ITT) and per-protocol (PP) analysis were used. The ITT population included all the participants who were randomized, while the PP population only included the participants who completed 5 days of DRV/c regimens. Variables were compared in the 2 study groups using t tests, the Mann-Whitney test, or the χ² test. The log-rank test was used to assess between-group differences in the duration of viral shedding. Hazard ratios and associated 95% confidence intervals were calculated with the use of a Cox proportional hazards model. All analyses were performed using STATA, version 12.0 (StataCorp, College Station, TX, USA).

RESULTS
From January 30, 2020, to February 6, 2020, a total of 30 participants were enrolled, of whom 18 (60%) were male, with a mean age (SD) of 47.2 (2.8) years (Figure 1). Fever was the most common symptom of onset, occurring in 86.7% (26/30) of the participants, followed by cough, which was present in 46.7% (14/30) of the participants. Less common symptoms included sore throat (2 [6.7%]), nausea (2 [6.7%]), fatigue (1 [3.3%]), diarrhea (1 [3.3%]), and headache (1 [3.3%]). The participants were admitted (IQR) at 4 (2–5) days after onset of symptoms. On admission, 11 patients in the DRV/c group and 8 patients in the control group still presented with fever; 33.3% (10/30) of participants showed unilateral pneumonia, and the others presented with bilateral pneumonia via chest computed tomography. Despite a difference that was not significant, more patients in the DRV/c group showed bilateral pneumonia (80.0% vs 53.3%). The clinical characteristics and laboratory findings of the 2 groups were comparable (Table 1). All participants completed the study, except 1 patient in the DRV/c group who progressed to critical condition on day 4 and withdraw from the study.

In the ITT analysis, the proportions of negative conservation of SARS CoV-2 at day 7 were 46.7% (7/15) and 60.0% (9/15) in the DRV/c and control groups (P = .72), respectively. In PP analysis, the proportions of negative conservation of SARS CoV-2 were 50.0% (7/14) and 60.0% (9/15) in the 2 groups (P = .72), respectively.

The viral clearance rate at day 3 was 20% (3/15) in both study groups. The proportion of negative PCR results was 26.7% (4/15) in the DRV/c group and 20% (3/15) in the control group at day 5. The median duration from randomization
to confirmed negative PCR was 8 days and 7 days, respectively. DRV/c was not associated with faster clearance of SARS-CoV-2 on oropharyngeal swab (hazard ratio, 0.82; 95% CI, 0.36–1.88) (Figure 2).

The 11 patients with fever in the DRV/c group defervesced at a median (IQR) of 4 (2–6) days, while 8 patients in the control groups defervesced (IQR) at 5 (2–6.8) days after randomization (P = .72). Computed tomography (CT) images from 7 patients in the DRV/c group and 4 patients in the control group showed worsening at day 7 (P = .45). Fourteen days after randomization, 1 participant in the DRV/r group progressed to critical illness (acute respiratory distress syndrome [ARDS]), while all the patients in

![Trial profile](figure1)

Figure 1. Trial profile. Abbreviation: DRV/c, darunavir/cobicistat.

### Table 1. Baseline Characteristics of the Intention-to-Treat Population

|                        | DRV/c Group       | Control Group    |
|------------------------|-------------------|------------------|
| Age, mean ± SD, y      | 51.5 ± 12.2       | 42.9 ± 17.7      |
| Sex male, No. (%)      | 9 (60)            | 9 (60)           |
| Days from 1 set of symptoms, median (IQR), d | 4 (2–5) | 4 (3–6) |
| Signs and symptoms at admission, No. (%) |                     |                  |
| Fever                  | 11 (80.0)         | 8 (86.7)         |
| Cough                  | 7 (47.7)          | 7 (47.7)         |
| Sore throat            | 1 (6.7)           | 1 (6.7)          |
| Nausea                 | 1 (6.7)           | 1 (6.7)          |
| Diarrhea               | 1 (3.3)           | 0                |
| Fatigue                | 0 (0)             | 1 (6.7)          |
| Chronic comorbidity    |                   |                  |
| Cardiovascular diseases, No. (%) | 4 (26.7) | 4 (26.7) |
| Diabetes, No. (%)      | 0                 | 2 (13.3)         |
| Radiological findings  |                   |                  |
| Bilateral pneumonia    | 12 (80)           | 8 (53.3)         |
| Unilateral pneumonia   | 3 (20)            | 7 (48.7)         |
| Laboratory findings    |                   |                  |
| White blood cells, mean ± SD, ×10^9/L | 4.6 ± 1.2 | 5.2 ± 1.6 |
| CD4 T-cell counts, mean ± SD, cells/μL | 495 ± 228 | 631 ± 365 |
| Alanine aminotransferase, median (IQR), U/L | 23 (14–38) | 21 (11–40) |
| Estimated glomerular filtration rate, median (IQR), mL/min/1.73 m² | 99.5 (78.8–110.6) | 114.4 (106–141.7) |
| C-reactive protein, median (IQR), mg/L | 17 (6.4–33) | 9.6 (3–173) |
| D-dimer, median (IQR), μg/mL | 0.43 (0.31–0.8) | 0.32 (0.28–0.71) |
| Lactate, median (IQR), mmol/L | 1.3 (0.9–1.6) | 1.6 (1.1–3.1) |

Abbreviations: DRV/c; darunavir/cobicistat; IQR, interquartile range.
the control group were stable ($P = 1.0$). This patient received me-
chanical ventilation on day 7. All patients were alive at day 14.

The frequencies of adverse events in the 2 groups were com-
parable. Diarrhea occurred in 20% (3/30) of participants in the 
DRV/c group and 13.3% (2/30) of participants in the control 
group, respectively. One patient in the DRV/c group developed 
anemia (hemoglobin levels dropped from 11.3 g/dL to 9.9 g/
dL). Elevated transaminase levels, defined as >2-fold of the 
upper limit of the normal range, were observed in 13.3% (2/30) 
of patients in the DRV/c group and 26.7% (4/30) of patients in 
the control group. Renal dysfunction (defined as estimated glo-
merular filtration rate <90 mL/min/1.73 m² in patients without 
chronic kidney diseases) occurred in 13.3% (2/30) of patients 
in the DRV/c group and 6.7% (1/30) of patients in the control 
group. All the adverse events were mild. No participants discon-
tinued DRV/c due to these adverse events.

**DISCUSSION**

In this pilot study, we found that the viral clearance rate at day 7 in the DRV/c group was comparable to that in the control group. In addition, the median duration of viral shedding from randomization was 8 days in the DRV/c group compared with 7 days in the control group, although there was no statistical significance. The only patient who progressed to ARDS and received mechanical ventilation was also in the DRV/c group. Taken together, our results do not suggest that 5 days of DRV/c could increase the proportion of negative conversion at day 7 vs standard of care alone, although it was well tolerated.

In conclusion, our pilot study does not suggest that 5 days of 
DRV/c could increase the proportion of negative conversion at 
day 7 vs standard of care alone, although it was well tolerated.

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**Author contributions.** J.C. and H.L. participated in the conceptualiza-
tion of the study. J.C., L.X., L.L., Q.X., Y.L., D.H., H.W., S.S., S.X., and 
Y.S. were study investigators and participated in the conduct of the study, 
including the recruitment and follow-up of participants. J.C., Y.S., and 
H.L. were involved in formal data analysis, methodology, project adminis-
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