Reply to: "Antiviral Activity and Safety of Darunavir/Cobicistat for Treatment of COVID-19"

Dear Editor,

Chen and colleagues evaluated the antiviral activity and safety of darunavir/cobicistat (DRV/c) in treating coronavirus-associated disease 2019 (COVID-19) in a randomized open-label study in 30 patients [1]. The authors did not observe any benefit in virological clearance, but there was no increase in side effects. However, severe/critical patients were not included; thus, as the authors stated, their findings may be not applicable to this population. Therefore, we report our results on the safety of darunavir/ritonavir (DRV/r) in 328 adults with COVID-19, most of whom had severe pneumonia.

In this study, we included HIV-negative patients consecutively hospitalized for COVID-19 between February 28 and March 29, 2020, who received the following standard of care (SOC): hydroxychloroquine (HCQ; 400 mg twice daily for 5–20 days), short-term initial antibiotic coverage, and anti-inflammatory treatment with tocilizumab and/or methylprednisolone. The patients admitted between February 28, 2020, and March 23, 2020, also received DRV/r 800/100 mg once daily for 5–10 days if not contraindicated (ie, severe cardiac or liver disease); as of March 24, 2020, we stopped using DRV/r based on data from recent studies showing inefficacy of lopinavir/ritonavir [2, 3].

Patients with a ratio between arterial oxygen partial pressure and fraction of inspired oxygen (PaO2/FiO2) ≤300 mmHg or pulse oxygen saturation ≤90% at resting were classified as severe cases [4]. The risk of developing at least an adverse event (AE) of any grade, defined according to the CTCAE scale version 5.0 [5], and the risk of death were evaluated according to the administration of DRV/r with a time-dependent Cox-regression analysis. *P* values <.05 were considered statistically significant. SPSS, version 21, was used for statistics. The study was approved by the Ethics Committee of the Ligurian Region (CER Liguria 163/2020). Off-label treatments were administered according to national and local regulatory procedures.

Overall, 328 adults with a mean age of 68 (±13.79) years were included. Of these, 223 (68%) patients had severe disease at baseline, 151 (46%) received DRV/r within 48 hours, and 177 (54%) did not receive DRV/r. Of these 177, 83 presented with COVID-19 after March 23. The median length of follow-up (interquartile range) was 21 (11–29) days.

No difference between patients who received or did not receive DRV/r was noted for age, sex, proportion of patients with PaO2/FiO2 ≤300 mmHg, or Charlson Comorbidity Index. Patients in the DRV/r group less frequently reported previous myocardial infarction (6, 3.9%, vs 25, 14.2%; *P* = .001), chronic heart failure (4, 22.2%, vs 14, 8%; *P* = .05), neutropenia (0 vs 5, 2.8%; *P* = .043), chronic liver disease (1, 7.7%, vs 12, 6.9%; *P* = .003), and long-term low-dose acetyl-salicylic acid therapy (0 vs 26, 14.8%; *P* < .0001).

Overall, 170/328 (48.8%) patients developed at least 1 AE of any grade, and 39/328 (11.9%) developed a grade 4–5 AE (ie, cardiovascular complications, n = 31, liver enzyme elevation, n = 2, and ventilator-associated pneumonia, n = 6), with similar rates between the DRV/r and non-DRV/r groups (57% vs 27.1%; *P* = .09; and 13.9% vs 10.2%; *P* = .3; respectively). The mean time to the first AE was 13.68 (±11.15) days. The most frequently reported AEs were liver enzyme elevations (40.4% DRVr vs 27.1% non-DRVr; *P* = .011), creatinine increase (9.3% vs 6.2%; *P* = .3), microbiologically documented bloodstream, pulmonary, or urinary infections (19.9% vs 17.5%; *P* = .59), cardiovascular disorders (13.2% vs 14.1%; *P* = .81), and mild diarrhea (11/151, 7.3%, vs 1/177, 0.6%; *P* = .001).

In the DRV/r group, diarrhea and liver enzyme elevations were regarded as possibly or probably associated with DRV/r. In no case was DRVr withdrawn due to an AE. In the multivariate time-dependent analysis, DRV/r did not affect the risk of developing AEs (Table 1).

Overall, 98 (29.9%) patients died of COVID-19. DRV/r did not affect the risk of death ($_{adj}$HR, 1.32; 95% CI, 0.85–2.06; *P* = .21) (Table 1).

Although we administered DVR with a different booster (ritonavir instead of cobicistat), our experience in a real-life cohort adds some evidence to the findings of Chen et al., given the large proportion of severe COVID-19 and the older age of patients we evaluated. First, a short-term course of DRV/r was well tolerated, as it did not increase the risk of AEs. Differences in concomitant SOC treatments, AE reporting, and study population might explain the higher grade 4–5 AE rate we found with respect to Chen et al. (11.9% vs 0%). Second, DRV/r did not influence overall mortality, while respiratory insufficiency, both at baseline and during treatment, and systemic inflammation did. Notably, Chen et al. did not report any death at 14 days of follow-up. The 29.9% in-hospital mortality rate we found may reflect the more severe clinical presentation and the older age of our cohort.

In conclusion, although well tolerated even in patients with severe COVID-19, DRV/r did not reduce mortality in COVID-19. Further studies are

Table 1. Multivariable Analyses for Predictors of Time to the First Adverse Event and Death in Patients With COVID-19

	Multivariable Analysis of Predictors of Adverse Events		Multivariable Analysis of Predictors of Death	
Factors	HR_{adj} (95% CI)	*P* Value	HR_{adj} (95% CI)	*P* Value
DRV/r, yes	1.24 (0.91–1.69)	.17	1.32 (0.85–2.06)	.21
Age (1-y change)[b]			1.07 (1.05–1.10)	<.001
Charlson index (1-point increase)[b]			1.15 (1.02–1.29)	.019
Previous myocardial infarction[b]			-	-
History of heart failure[a]	1.70 (0.86–3.38)	.13	3.25 (1.59–6.64)	.001
COPD[a]	1.88 (1.00–3.53)	.05		
Connective tissue disease[a]	3.12 (0.98–9.96)	.055		
Peripheral vascular disease[b]			-	-
History of a cerebrovascular accident[b]			-	-
Dementia[b]			-	-
Peptic ulcer disease[b]	-	-		
Neutropenia[b]			8.28 (2.21–31.08)	.002
Hypertension[a,b]	1.38 (1.01–1.89)	.040	-	-
Diabetes mellitus[b]			1.70 (1.02–2.84)	.041
Cardiac disease[b]			-	-
Chronic liver disease[b]			-	-
Chronic renal disease[b]			-	-
Ongoing leukemia/lymphoma[b]			-	-
Long-term treatment with steroids at home[b]			2.24 (1.22–4.14)	.01
Long-term low-dose acetyl-salicylic acid therapy[b]			-	-
Long-term treatment with anticoagulants[b]			2.27 (1.24–4.18)	.008
Time from symptoms (>7 vs ≤7 d) to start of HCQ[b]			-	-
PaO_2/FiO_2 <300 vs ≥300[a,b]	-	-	2.36 (1.31–4.25)	.004
Noninvasive mechanical ventilation[a,b]	1.51 (1.01–2.26)	.047	2.00 (1.13–3.53)	.017
Invasive ventilation[a,b]	2.25 (1.51–3.35)	<.001	3.26 (1.85–5.77)	<.001
Interleukin-6 (1-unit increase on log scale)[b]	1.15 (1.01–1.32)	.044	1.36 (1.12–1.67)	.002
Ferritin (1-unit increase on log scale)[b]			1.35 (1.02–1.81)	.035
C-reactive protein (1-unit increase on log scale)[b]			1.25 (0.93–1.67)	.14
Tocilizumab[a]	1.59 (1.06–2.38)	.024		
Remdesivir[a]	-	-		

The following variables were collected and included in all the analyses: demographic (ie, sex, age), clinical (ie, Charlson index, comorbidities, long-term treatments, time interval from onset of symptoms to start of HCQ, arterial oxygen partial pressure, PaO_2/fraction of inspired O_2,FiO2); laboratory parameters at baseline; type and timing of mechanical oxygen supplementation (invasive/noninvasive NIV); additional treatments (remdesivir, tocilizumab, and methylprednisolone). Mechanical oxygen supplementation and additional treatments were regarded as time-dependent covariates.

Abbreviations: $_{adj}$HR, adjusted hazard ratio; COPD, chronic obstructive pulmonary disease; DRV/r, darunavir/ritonavir; PaO_2/FiO_2, arterial oxygen partial pressure/fraction of inspired oxygen.

[a]Variables associated with developing adverse events in the univariate analysis with a *P* value <.15 and entered into the multivariable model.

[b]Variables associated with death in the univariate analysis with a *P* value <.15 and entered into the multivariable model.

warranted to establish the best management strategy.

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