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LETTER TO THE EDITOR

Authors' Reply to Cattaneo et al.: "Comment on: Comparative Population Pharmacokinetics of Darunavir in SARS-CoV-2 Patients vs. HIV Patients: The Role of Interleukin6"

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We read with interest the letter of Cattaneo et al. commenting on our research and providing data on darunavir trough concentrations in a small cohort of patients who were co-infected with human immunodeficiency virus (HIV) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. In our population pharmacokinetic modelling, it was shown that interleukin-6 (IL-6) was the only covariate significantly associated with darunavir apparent clearance among patients with SARS-CoV-2 [2]. Decreased darunavir apparent clearance with increased exposure was documented only in patients with SARS-CoV-2 with severe disease (Phase 2 or 3 according to Siddiqi classification [3]). The CART analysis showed that patients with SARS-CoV2 with IL-6 ≥ 18 pg/mL had significantly lower darunavir apparent clearance compared with both patients with SARS-CoV-2 and patients with HIV with IL-6 levels below this threshold (2.78 vs 7.24 vs 9.75 L/h, respectively, $p < 0.001$) (Table 1). This was attributed to a downregulation of cytochrome P450 3A4-mediated darunavir metabolism promoted by high IL-6 levels, as supported by evidence that high levels of many cytokines may modulate several cytochrome P450 isoenzyme activities [4].

Cattaneo et al. first showed that darunavir trough concentrations were not increased in a cohort of six patients who were co-infected with HIV and SARS-CoV-2 (836 ng/mL [409–1523 ng/mL]), and were almost similar to those observed in a comparator group of 130 patients with HIV without SARS-CoV-2 infection (1273 ng/mL [734–1954 ng/mL]) and to healthy volunteers [1]. The median IL-6 level was 17 pg/mL (interquartile range 4–53 pg/mL) among co-infected patients with HIV/SARS-CoV-2 and was not measured in the control cohort of patients with HIV. On the basis of these findings, they supposed that in patients co-infected with HIV and SARS-CoV-2, the presence of a pro-inflammatory state may not result in increased darunavir exposure, and that the increased darunavir exposure that we documented in patients with SARS-CoV-2 could be switched off in this patient population by the concomitant presence of HIV infection. Unfortunately, no possible explanation concerning the potential mechanism by which HIV should mitigate the effects of SARS-CoV-2 disease on cytochromial enzyme activity was provided.

Although we respect the opinion of Cattaneo et al., we believe that this assumption is quite difficult to be addressed with this small cohort, considering also that no pharmacokinetic analysis could have been performed. Noteworthy, the median value of IL-6 was quite low in the six co-infected patients with HIV/SARS-CoV-2, and this may support our contention that in the absence of a major pro-inflammatory response no relevant downregulation might have occurred

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Table 1 Comparison of darunavir plasma exposures in the cohorts of patients with SARS-CoV-2 with IL-6 ≥ 18 pg/mL and with IL-6 < 18 pg/mL, and in patients with HIV [2]

	Patients with SARS-CoV-2 with IL-6 ≥ 18 pg/mL	Patients with SARS-CoV-2 with IL-6 < 18 pg/mL	Patients with HIV	*p* value
Patients (*n*)	20	10	25	–
IL-6 (pg/mL)	51.0 (32.5–160.3)°†	8.00 (2.3–10.0)°	2.0 (2.0–2.8)†	< 0.001
Darunavir trough concentrations (ng/mL)	7715 (4960.2–10343.3)°†	1896 (927.8–2596.9)°	1010 (550.0–2112.0)†	< 0.001
Darunavir CL/F (L/h)	2.78 (2.16–4.47)°†	7.24 (5.88–10.38)°	9.75 (8.45–13.79)†	< 0.001

Data are expressed as median (interquartile range). *p* value calculated with analysis of variance statistics. Symbols refer to statistically significant differences between groups after post-hoc Bonferroni correction

CL/F apparent clearance, *HIV* human immunodeficiency virus, *IL-6* interleukin-6, *SARS-CoV-2* severe acute respiratory syndrome coronavirus 2

in these patients. Unfortunately, Cattaneo et al. did not provide any data concerning the severity of illness among these co-infected patients with HIV/SARS-CoV-2, a finding that might have corroborated or refuted our hypothesis.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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