Prediction of lopinavir/ritonavir effectiveness in COVID-19 patients: a recall of basic pharmacology concepts

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Dear Editor,

A recent population pharmacokinetic analysis of lopinavir/ritonavir concentrations collected in 13 coronavirus disease 2019 (COVID-19) patients demonstrated that a dose of lopinavir of 400 mg twice daily led to 40% of patients below the minimum effective concentration (MEC); the authors proposed that the use of lopinavir of 1200 mg twice daily would reduce this proportion to 22% [1]. We believe that these findings may have been biased by a misinterpretation of some basic pharmacologic concepts, as detailed below.

Choy and coworkers have initially reported the *in vitro* inhibitory activity of lopinavir against SARS-CoV-2 virus in Vero E6 cells with an estimated 50% effective concentration (EC₅₀) at 26 μ M [2]. However, the EC₅₀ is not the ideal pharmacodynamic parameter because at this concentration, 50% of the virus still replicates; therefore, the EC₉₀ (or the EC₉₅) should preferably be considered to get closer to the MEC. Moreover, two other factors need to be considered for the proper prediction of lopinavir effectiveness in inhibiting SARS-CoV-2. Firstly, lopinavir circulates in the body largely bound to plasma proteins (>95%) and its inhibitory activity on virus replication relies on the 5% or less free drug fraction. Therefore, the EC₅₀ and EC₉₀ need to be adjusted for serum protein content. The second important variable is represented by the quantification of the optimal drug concentrations at the site of infection. Accordingly, we have recently estimated the concentrations of lopinavir required to inhibit *in vivo* SARS-

CoV-2, taking into consideration the 90% of virus inhibition, the drug protein binding, the tissue drug distribution, and the plasma drug concentrations measured in COVID-19 patients treated with the conventional lopinavir/ritonavir 400/100 mg twice daily dose [3, 4]. Based on our predictions, the concentrations of lopinavir required to inhibit SARS-CoV-2 replication in plasma, epithelial lining fluid, and cerebrospinal fluid are, respectively, 200-fold, 20-fold, and 2000-fold higher than those measured *in vivo*. These findings provide solid evidence that the lopinavir dose required to inhibit SARS-CoV-2 replication is clinically unachievable (i.e., it would take a dose tens/hundreds of times greater than that currently used), clearly arguing against a role of this drug in the treatment of COVID-19. Remarkably, the same findings have been consistently reported also by other independent research groups [5, 6].

The population pharmacokinetic modeling developed by Alvarez et al. is based on the assumption that “lopinavir presented antiviral effect against SARS-CoV-2 virus with a MEC of 26 μ M.” We believe that the authors have misinterpreted the MEC with the EC₅₀. These two pharmacodynamic parameters are not superimposable for the reasons explained above. As additional drawbacks, their estimations did not take into account the protein-adjusted EC₉₀ and, most importantly, the issues of drug tissues distribution. Their conclusion that the use of a triple dose of lopinavir would result in subtherapeutic drug concentrations only in 22% of patients is based on the estimation of the amount of plasma lopinavir concentrations resulting above the EC₅₀, disregarding lopinavir exposure in key compartments such as lung and central nervous system.

Recently published clinical trials have demonstrated the ineffectiveness of lopinavir in COVID-19 patients [7], thus preventing any centers from the potential use of lopinavir/ritonavir at a dose of 1200 mg twice a day as proposed by Alvarez et al. These suggestions, if adopted, could have potentially increased the risk for COVID-19 patients to experience episodes of lopinavir-related toxicity.

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Compliance with ethical standards

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

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