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LETTER TO THE EDITOR

Reply to the letter to the Editor "Prediction of lopinavir/ritonavir effectiveness in COVID-19 patients: a recall of basic pharmacology concepts"

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We thank Cattaneo et al. for their comments regarding our lopinavir/ritonavir calculations and dosing recommendations in our recently published study [1]. However, we do not agree with them for various reasons.

The adaptations of the 50% effective concentration (EC_{50}) made by Cattaneo et al. [2, 3] have numerous weaknesses. They are based on several flawed assumptions and, moreover, they multiply with each other, greatly increasing inaccuracies.

First, they consider that "the EC_{50} is not the ideal pharmacodynamic parameter because at this concentration 50% of the virus still replicates". This statement is correct but SARS-CoV-2 is not HIV. Indeed, some patients are able to develop a clinical response leading to a cure with a disappearance of the virus even without any treatment. Thus, a compound able to decrease the viral replication may have some interest for the patients helping them to respond to the infection. Nevertheless, the authors decided to estimate the EC_{90} from the published EC_{50} [4]. This computation depends on the hill slope factor and they decided to set this value to 1. However, a close look to the figure 1B published by Choy et al. [4] suggests a higher value because the profile depict a strong steepness. Using a web digitizer (https://apps.automeris.io/wpd/) and a non-linear regression implemented with R, it is possible to observe that a value higher than 2 might be required to fit the data. The EC_{90} values obtained with an EC_{50} of 26 μM but with a hill slope factor of 2, 3, and 4 lead to 78, 54, and 45 μM, respectively. It is clear that the value of 234 μM proposed by the authors for the EC_{90} is not appropriate.

Second, we agree that lopinavir is highly bound in plasma. But it cannot be stated that its inhibitory activity on the virus replication relies on the free drug fraction. This is only true if lopinavir penetration into the cell is passive. To our knowledge, this assertion is not known for the targeted cells in COVID-19 disease. The authors suggest that an adjusted EC_{90} should be estimated for the free concentration. However, the EC_{50} estimated by Choy et al. [4] was not based on a free lopinavir concentration but on a media containing albumin (2% fetal bovine serum). According to the article published by Boffito et al. [5], the EC_{50} estimated by Choy et al. [3] should be adjusted to a free IC_{50} before being compared to a free in vivo concentration.

Third, the authors suggest to extrapolate EC_{90} to the site of infection. They used a result obtained on one patient, at one sampling time on epithelial lining fluid (ELF) [6]. This assumption is not appropriate for several reasons:

- If the epithelial lining fluid (ELF) is the site of infection (as suggested by the authors), it is not the site of action of lopinavir. It could be more relevant to consider the lopinavir interstitial fluid concentrations. No data allows to suggest that ELF and interstitial fluid have similar lopinavir concentrations. Furthermore, the mechanism of action of lopinavir is intracellular not in the bronchoalveolar lavage fluid.
- Clinical results based on one individual for a compound known to have a wide inter-individual variability are questionable.
- The concentration versus time profile in plasma and lung is probably not parallel and using a single sampling time

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to resume all the characteristics of the lung pharmacokinetic is a doubtful hypothesis.

To conclude, we agree that the appropriate target for lopinavir in COVID-19 patients remains to be defined. In our opinion, fewer assumptions are better and it is more appropriate to limit them before drawing definitive statement that a compound is effective or not in a new indication. Our conclusion was based on validated data and suggested that the dose used of lopinavir was too low in COVID-19 disease [1]. If this compound should be further tested in a clinical trial, a higher dose than that used in HIV disease should be considered and especially with a loading dose. A close safety monitoring is a relevant warning when using a drug in a new indication at doses higher than those usually used. Discarding a compound solely based on multiplication of assumptions would lead to a missed opportunity. Because repurposing is going to be a new challenge, proper methods should be used with caution.

Compliance with ethical standards

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

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