RESPONSE LETTER TO THE EDITOR

Response to "Dose Rationale for Favipiravir Use in Patients Infected With SARS-CoV-2"

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Dear Editor,

We appreciate the letter by Eloy *et al.* for their comments and complement regarding our review.[1,2] Two independent *in vitro* studies indicated that favipiravir (T-705) inhibited severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) replication in Vero E6 cells with half-maximal effective concentration (EC_{50}) values of 61.88 μM (9.4 μg/mL)[3] and > 100 μM (15.7 μg/mL),[4] respectively. Data from the authors' group suggests an EC_{50} value in the range 40–80 μg/mL (X. de Lamballerie & F. Touret, unpublished results). I agree with the authors' assumption that favipiravir shows similar EC_{50} against SARS-CoV-2 and Ebola virus (EBOV). As favipiravir is a prodrug that requires metabolic activation through ribosylation and phosphorylation in the host cells to form its triphosphate form (favipiravir-RTP), we think that variation in favipiravir activation by the cultured cells may, at least partially, contribute to the difference in the *in vitro* EC_{50} among studies.

Based on the EC_{50} from an *in vitro* study, plasma concentrations obtained from the JIKI trial, and simulations from a pharmacokinetic model, the authors suggested a higher favipiravir dose (loading dose of 2,400 mg b.i.d. on day zero, followed by a maintenance dose of 1,600 mg b.i.d. for 9 days) to achieve a pharmacologically relevant target trough concentration of 40–80 μg/mL in coronavirus disease 2019 (COVID-19).[1] An increase in the maintenance dose definitely increases the overall drug exposure. However, as mentioned above, favipiravir is a prodrug that requires metabolic activation, whereas tissue and cellular exposure of the activate metabolites favipiravir-RTP is more critical. Self-inhibition of its metabolism to the formation of T-705M1 in the liver after continuous use may result in an increase in circulating T-705/T-705M1 ratio, and, thus, facilitate the uptake and activation of favipiravir in the tissues.[2] A decrease in trough plasma concentrations of favipiravir does not mean a decreased exposure of the active metabolite favipiravir-RTP in the tissues. We think that this is an issue that deserves further study and discussion. A randomized clinical trial has evaluated the safety and efficacy of favipiravir in patients with COVID-19 in China.[5] A dose regimen including 1,600 mg b.i.d. on day 1, followed by 600 mg b.i.d. for 7–10 days from day 2 was adopted in the trial in COVID-19 patients. The results showed some evidence of efficacy, as indicated by 7 day's clinical recovery rate, time of fever reduction, and cough relief in ordinary patients.[5] It is noteworthy that 31.9% of the patients showed antiviral adverse effects, including increased serum uric acid, abnormal liver function tests, and digestive tract reaction, albeit these adverse effects were mild and manageable.[5] Although the suggested high maintenance dose by Eloy *et al.* has been practiced in a few EBOV-infected patients, this high dose should be used with caution in COVID-19. Close monitoring of the concentrations of the drug, especially for the active metalite favipiravir-RTP, if possible, and clinically relevant adverse events are suggested when favipiravir is used with a higher dose.

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CONFLICT OF INTEREST

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