Comment on: Favipiravir, an antiviral for COVID-19?

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Sir,

We have read with interest the letter by Coomes and Haghyban,1 which presents favipiravir as a potential treatment for COVID-19. The authors, based on the results of in vitro studies and benefit shown in a clinical trial of this drug, state that there is an urgent need for more clinical studies of favipiravir. However, the authors only praise the results of the clinical trial of favipiravir,2 but they do not give information about the methodological flaws of the study. In our opinion, it is important to present the strengths and limitations of the body of evidence to readers. That is why in this letter we present some methodological aspects of this clinical trial that should be considered when interpreting the results.

First, a study must always choose endpoints that can show a real benefit for the patient; these are known as critical endpoints. The US FDA considers critical clinical endpoints as those that measure how a patient ‘feels, functions, or survives’;3 some examples of these endpoints are mortality or a symptom score. Nevertheless, this study made the debatable decision to include only non-critical endpoints (decrease in the average time to viral clearance and improvement in the chest tomography of COVID-19-infected patients). Even though they show a statistical difference, it is hard to argue that there is a clinically significant difference between both groups.

Second, as a non-randomized trial, it is not possible to isolate the effect of the intervention. This limitation can be exemplified by the difference between patients in their number of lymphocytes in the two arms of the trial, with a P value for the difference near 0.05. These lower levels of lymphocytes have been considered a predictive factor for severity in COVID-19 infection,4 so we could hypothesize that the groups were not in reality that comparable. Similarly, in the article there is no information about the comorbidities of the participants, which may have been different between the intervention arms and hence influenced the outcomes. Nevertheless, it is mentioned that the authors adjusted the multivariate model with a variable named ‘underlying disease’. It is unacceptable not to include such important information, which could change the interpretation of the results.

Third, the only statistically significant difference was at Day 14 in both outcomes. Nevertheless, most mildly affected patients will clear the virus at Day 10 and only those with severe disease have persistence of the virus,5 and we cannot discard the possibility that a selection bias influenced the results of the study.

Finally, the authors of this trial state that it was unethical to conduct a randomized clinical trial: ‘it was ethically unacceptable to allocate patients to receive different experimental drugs, and a randomization process was infeasible’.2 We disagree with this statement. In the current situation, what the world needs is the generation of the best evidence as soon as possible to avoid the unnecessary exposure of patients to futile experimental interventions. Randomized trials have already been done with success in this pandemic setting,6 proving that it is possible to overcome barriers and conduct high-quality research in this context.

In combination, these limitations do not allow the conclusion that there was a real benefit in the intervention arm or that this drug is as promising as the authors of the letter have stated.1 It is our responsibility as medical researchers to conduct research of the highest quality possible, and always be mindful of methodological flaws and inform readers of them.

In summary, the authors provided an incomplete summary of the only available trial of favipiravir. It is important to always state the methodological flaws of the existing studies to inform readers that the results are not entirely reliable. The scientific community must always maintain their supervisory role and be very careful to avoid coming to incorrect conclusions.

Transparency declarations

None to declare.

References

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