

Nuanced findings for a large experimental treatment trial for Ebola virus disease

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While not conclusive, valuable research generated through researching an experimental treatment for Ebola virus disease in Guinea during the recent Ebola outbreak will support future research into treating Ebola virus disease, according to Prof. Denis Malvy from INSERM, France and a large team of international researchers in a new Research Article published in this week's *PLOS Medicine*.

Ebola virus disease is a highly lethal condition for which no specific treatment has proven efficacy. In September 2014, while the recent Ebola outbreak was at its peak, the World Health Organization released a short list of drugs suitable for Ebola virus disease research that included favipiravir, an antiviral developed for the treatment of severe influenza. To test the feasibility and acceptability of an emergency trial in the context of a large Ebola outbreak and to collect preliminary data on the safety and effectiveness of favipiravir in reducing mortality and viral load in patients with Ebola virus disease, a multinational team of researchers conducted a study in Guinea called JIKI (meaning "Hope" in the Malinke language). Because of the exceptional circumstances of the recent Ebola outbreak the study was a historically controlled multicenter non-randomized trial, in which all 126 participants received favipiravir along with standardized care.

The results of the study indicate that monotherapy with favipiravir is unlikely to be effective in patients with very high viremia (Ebola virus in the blood) and merits further investigation in patients with intermediate to high viremia. This conclusion is based on two findings, namely, the

observed mortality rates and the dynamics of Ebola virus RNA measured in the blood of patients on treatment. In patients with very high viremia, mortality was 7% higher than expected based on historical Ebola cases and Ebola virus measurements did not decrease. This suggests that any future trial is unlikely to demonstrate any benefit of favipiravir in these patients. In patients with lower viremia, mortality was 33% lower than expected based on historical controls and viremia decreased rapidly on treatment but the study was not able to attribute this decrease to favipiravir. The trial was non-randomized and the 95% confidence interval of mortality overlapped with what was expected from historical Ebola patients. Therefore, this finding does not prove that favipiravir was effective in these patients but only suggests that the question remains open and gives some indication on how to better address it.

The authors conclude, "in the midst of an Ebola outbreak, researchers may be faced with elements that make them feel that randomizing patients to receive either standard care or standard care plus an experimental drug is not ethically acceptable. In these rare circumstances, it can be decided to not run a trial and to wait for more favorable conditions, or to run a non-randomized trial. In this pilot experience, we did the latter. Our conclusions are nuanced. On the one hand, we cannot conclude on the efficacy of the drug, and our conclusions on tolerance, although encouraging, cannot be as firm as they would have been if we could have used randomization. On the other hand, we learned a lot about how to quickly set up and run a trial in such unusual circumstances and in close relationship with the community and non-governmental organizations, we integrated research into care so that it improved care, we rapidly generated and shared with the scientific community intermediate data that were useful for designing Ebola research, and we gathered evidence that will allow researchers to base further trials on strong preliminary assumptions."

More information: Daouda Sissoko et al. Experimental Treatment

with Favipiravir for Ebola Virus Disease (the JIKI Trial): A Historically Controlled, Single-Arm Proof-of-Concept Trial in Guinea, *PLOS Medicine* (2016). [DOI: 10.1371/journal.pmed.1001967](https://doi.org/10.1371/journal.pmed.1001967)

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