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Title: Modélisation de l'effet du favipiravir sur la dynamique viro-immunologique de la maladie à virus Ebola et implications pour son évaluation clinique

Abstract: In spite of recurrent outbreaks, no therapeutics with demonstrated clinical efficacy are available in Ebola virus disease. Based on experimentations performed by Reaction! Consortium in mice and macaques, this thesis aimed to characterize the effect of an antiviral drug, favipiravir, using mechanistic mathematical models of the infection and associated immune response. The approach to build models and estimate parameters relied on nonlinear mixed effect models. The first project of this thesis explored the concentration-effect relationship on the viremia in mice. Then, a second project allowed to characterize the pharmacokinetics of favipiravir in macaques, underlying dose and time non linearity, and to identify relevant dosing regimen for efficacy experiments in infected animals. Once these experiments completed, the integration of the virological and immunological data into a joint model shed light on the effect of favipiravir. The moderate inhibition of the viral replication resulting from the favipiravir plasma concentrations was enough to limit the development of a deleterious inflammatory response, and thus improve the survival rate of treated macaques. Simulations performed with this model underlined the crucial impact of the treatment initiation delay on survival. These results encourage the pursuit of the clinical evaluation of favipiravir in prophylaxis or post exposure trials. Finally, a last project demonstrated the lack of benefit of ribavirin addition to favipiravir in Ebola virus disease.

Key words: Nonlinear mixed effects models, pharmacokinetics-pharmacodynamics, viral kinetics, Ebola virus disease, favipiravir, antivirals