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Dose regimen of favipiravir for Ebola virus disease

Although several antivirals have shown efficacy against Ebola virus infection in vitro or in animal models, none of them has been yet assessed in human beings with Ebola virus disease.

Potential drug candidates include favipiravir,[1] a nucleotide analogue approved for novel or re-emerging influenza in Japan. This year, results of two independent studies in mice infected with Ebola virus showed that the initiation of 150 mg/kg favipiravir twice a day within 6 days of infection induced a rapid virus clearance, reduced biochemical parameters of disease severity, and led to 100% survival.[2,3] Moreover, favipiravir had a good safety profile in thousands of patients worldwide, is immediately available, and can be used orally, leading the French drug safety agency (ANSM) to approve the compassionate use of favipiravir in patients with Ebola virus disease. Here we explain the approach we used to propose a dose regimen in a forthcoming trial in Guinea that is assessing survival in adults with Ebola virus disease who receive favipiravir.

First we used the dose regimen used to successfully treat mice to estimate target plasma favipiravir concentrations for human patients. Using data provided by the manufacturer, we showed that, in mice, 150 mg/kg every 12 h led to mean daily minimal concentrations (C_{min}, 12 h post-dosing) of 5 μg/mL, average concentrations (C_{ave}, defined by the area under the concentration curve from 0 h to 24 h divided by 24 h) of 58 μg/mL, a half-life of 1·8 h, and maximal concentrations (C_{max}) of 200 μg/mL. Since 10% of favipiravir is bound to plasma proteins in mice, unbound average (C_{ave_u}) was therefore targeted to 52 μg/mL, and minimum concentrations (C_{min_u}) to 4·5 μg/mL. Of note, 52 μg/mL is higher than the 99% inhibitory concentration with Zaire Ebola virus Mayinga 1976 strain (estimated to be 29 μg/mL).[3] Plasma protein binding in human beings was 54%; therefore, plasma C_{min} and C_{ave} were targeted to 10 μg/mL and 113 μg/mL, respectively.

Second, we used the pharmacokinetic model developed by the manufacturer in human beings with the parameter values estimated in US healthy volunteers to assess a dose regimen that could achieve these targeted concentrations. Simulations were done with various maintenance doses of 1000 mg, 1200 mg, and 1800 mg twice a day and led to median C_{ave} at a steady state of 66·8 μg/mL (90% prediction interval 57·2–76·5), 83·3 μg/mL (72·2–95·3), and 134·4 μg/mL (115·9–152·0), respectively. Although the dose of 1200 mg twice a day gave a slightly lower C_{ave} than targeted, it minimised the chance of relapse (C_{min} of 57 μg/mL) and remained in the range of exposures previously assessed in human beings with good tolerance.

Since viral spread has to be blocked as soon and as strongly as possible after appearance of first symptoms, we assessed several loading dose strategies on day 1 to rapidly achieve high levels of exposure. In view of the short half-life of favipiravir, a dose of 2400 mg twice a day led to a low median C_{min} of 4·3 μg/mL (90% prediction interval 0·6–15·6). Rather, concentrations achieved with a regimen of 2400 mg, 2400 mg, and 1200 mg every 8 h allowed us to achieve a C_{min} at 8 h of 9·8 μg/mL (2·9–23·5) and a C_{min} at 16 h of 45·2 μg/mL (12·9–85·1).

To summarise, we describe the method used to propose a relevant dose regimen of favipiravir to be assessed in patients with Ebola virus disease, in a context where trials are urgently needed. Our approach combined data on favipiravir efficacy against Ebola virus in vitro and in vivo with data provided by the manufacturer on favipiravir pharmacokinetics in uninfected mice and human beings. On the basis of these elements, we will assess favipiravir in adults with a loading dose of 2400 mg, 2400 mg, and 1200 mg every 8 h on day 1, and a maintenance dose of 1200 mg twice a day afterwards. Of note, this dose regimen is 50% greater than the one in the phase 3 trials of favipiravir for influenza in the USA (1800 mg twice a day on day 1, 800 mg twice a day on day 2–5). To reduce the chance of relapse in Ebola virus disease, we decided to give the treatment for 10 days, which corresponds to the time needed for an effective antibody response.[4]

Although modelling is a valuable method to optimise the search of a dosing regimen, it is not a substitute for clinical data. Tolerance, virological, and pharmacokinetic data will be obtained during the trial to help to refine the dose regimen.

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