Modeling of moxifloxacin pharmacokinetics and fecal microbiota disruption in healthy volunteers

Authors: Charles Burdet1,2, Thu Thuy Nguyen1, Jean de Gunzburg3, Stéphanie Ferreira4, Annie Ducher3, Xavier Duval1,2, Marina Varastet3, Antoine Andremont1,2, France Mentré1,2

Affiliations: (1) INSERM & Paris Diderot University, UMR 1137, Paris, France; (2), AP-HP, Bichat Hospital, Paris, France; (3) Da Volterra, Paris, France; (4) Genoscreen, Lille, France

Objectives: Antibiotic administration has a major impact in disrupting microbiota composition [1]. We developed a joint model of plasma and fecal pharmacokinetics of moxifloxacin, a fluoroquinolone antibiotic, after oral administration in humans, and of moxifloxacin effect on bacterial richness observed within the intestinal microbiota.

Methods: 22 healthy volunteers were included in a RCT (sponsor Da Volterra) among which 14 received moxifloxacin (400 mg orally OAD) from D1 to D5. Moxifloxacin plasma concentrations were assayed at D1 and D5. Fecal samples were obtained before treatment and up to D37 for measurements of free moxifloxacin concentrations and microbiota analysis by 16S rRNA gene profiling. Bacterial richness was evaluated using the number of operational taxonomic units (OTUs). NLME were used to analyze the plasma pharmacokinetics of moxifloxacin and its fecal excretion, and to evaluate the effect of fecal concentration on bacterial richness. Analysis was performed using the Monolix software. Model selection was performed by visual inspection of goodness of fit plots and the Bayesian Information Criteria.

Results: MOX plasma concentrations were best described by a 2-compartment model with transit compartments for absorption and linear elimination. Fecal concentrations were modeled using a transit compartment between plasma and feces, with reabsorption from the fecal compartment to the central compartment. The effect of moxifloxacin on the number of OTUs was best described by a turn-over model, with an Emax model where fecal moxifloxacin concentration increased the loss rate. Goodness-of-fit was satisfactory.

Conclusions: We developed the first joint model of the co-evolution of individual plasma and fecal exposure to an antibiotic, and of bacterial richness observed in the intestinal microbiota. Analysis of other microbiota metrics is necessary to refine moxifloxacin effects on the microbiota.

References: