Modelling helps understanding reduction of mortality provided by DAV131A in a hamster model of moxifloxacin-induced *Clostridium difficile* colitis

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1. BACKGROUND

- *Clostridium difficile* is considered as an immediate public health threat [1].
- Antibiotic administration is a leading cause of *C. difficile* intestinal infection [2].
- DAV131A adsorbs antibiotics residuals reaching the small and large intestine, and reduces mortality in a hamster model of moxifloxacin-induced *C. difficile* colitis [3, 4] where moxifloxacin (fMOX) is given by subcutaneous (SC) route and DAV131 by oral gavage.

We investigated the relationships between the dose of DAV131A administered, free fecal concentration of moxifloxacin (fMOX) and mortality.

2. MATERIALS

- 215 male Syrian hamsters included in a total of 3 studies whose data were pooled for this analysis

![Figure 1. Studies design](Image 49x1989 to 260x2232)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Follow-up</th>
</tr>
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<tbody>
<tr>
<td>MOXIFLOXACIN (SC route)</td>
<td></td>
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<tr>
<td>DAV131A (oral route)</td>
<td>End of study</td>
</tr>
</tbody>
</table>

- DAV131A daily dosing:
  - 0 mg/kg/day (controls, n=35)
  - 200 mg/kg/day (n=10)
  - 600 mg/kg/day (n=50)
  - 1200 mg/kg/day (n=50)
  - 1800 mg/kg/day (n=50)

- DAV131A administration schedule:
  - 8 ID regimen (n=165): DAV131A administered at H_{4}/H_{6}. Various schedules for D_{i}:
    - Before MOX administration (H_{i}/H_{6}, n=115, 55 with 1 dose at H_{3}, D_{1}):
    - Together with MOX administration (H_{i}/H_{6}, n=20):
    - After MOX administration (H_{i}/H_{6}, n=30):
  - TID regimen (n=15, all with 1 dose at H_{5}, D_{1}):
  - Administration at H_{3}/H_{6}/H_{8}:
  - fMOX measured by microbiological assay (*B. subtilis* ATCC 6633)

3. STANDARD STATISTICAL ANALYSES

3.1 Methods

- Mortality rates at D_{0} compared according to DAV131A daily dose using non-parametric Wilcoxon test
- Association between fMOX and DAV131A daily dose using Spearman correlation

3.2 Results

- Data from 210 hamsters available for analysis

![Figure 2. Mortality decreased significantly with increasing daily doses of DAV131A (p<10−15)](Image 870x81 to 1582x668)

- Predicted relationship between DAV131A daily dose and mortality

![Figure 3. fMOX decreased significantly with increasing daily doses of DAV131A (p<10−9)](Image 3114x2109 to 3324x2195)

4. MODELLING ANALYSIS

4.1 Methods

- Joint model of DAV131A daily dose, fMOX and mortality (estimation by maximum likelihood using data of all hamsters)
- Linear model between DAV131A daily dose and fMOX
  - fMOX_{max}, mean fMOX in absence of DAV131A; D_{0}, dose allowing for 50% of maximal effect; γ, sigmoidicity coefficient
  - \[ fMOX = fMOX_{max} \times \left( 1 - \frac{1}{1 + \exp\left( -\gamma \times \frac{D}{D_{0}} \right)} \right) \]
- Studied covariates of D_{0}:
  - DAV131A intake at H_{4}, at D_{0}, number of DAV131A daily intake and DAV131A administration schedule
- Logistic model between fMOX and mortality
  - \( \logit(\theta) = \alpha + \beta \times (fMOX) \)

4.2 Results

- Predicted relationship between DAV131A daily dose and fMOX

![Figure 4. Predicted relationship between DAV131A daily dose and fMOX](Image 1716x447 to 2570x805)

- Predicted relationship between DAV131A daily dose and mortality rate

![Figure 5. Predicted relationship between DAV131A daily dose and fMOX](Image 1716x447 to 2570x805)

![Figure 6. Predicted relationship between DAV131A daily dose and mortality rate](Image 1716x447 to 2570x805)

5. PREDICTIONS

5.1 Methods

- Use of joint model to compute fMOX and DAV131A daily dose needed to obtain various rates of mortality (50%, 10%, 5% and 1%)

5.2 Results

<table>
<thead>
<tr>
<th>Mortality rate</th>
<th>fMOX (µg/mL)</th>
<th>DAV131A dose needed (mg/kg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50%</td>
<td>610.9</td>
<td>238.2</td>
</tr>
<tr>
<td>10%</td>
<td>103.1</td>
<td>12.0</td>
</tr>
<tr>
<td>5%</td>
<td>6.8</td>
<td>4.4</td>
</tr>
<tr>
<td>1%</td>
<td>0.4</td>
<td>0.3</td>
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6. CONCLUSIONS

- DAV131A provides a dose-dependent reduction of mortality in a hamster model of moxifloxacin-induced *C. difficile* infection
- Observed reduction of mortality from 100% (95%CI, 90-100) in controls to 0% (95%CI, 0-6) for daily doses of 1200 mg/kg/day and higher
- First product to exhibit such level of protection against mortality
- Wide potential spectrum of protection through adsorption of most antibiotics in vitro
- Modelling approach allowed to investigate the mechanism of action of DAV131A
- Dose-dependent reduction of the colonic concentration of moxifloxacin
- Ongoing studies
  - In animals, other antibiotics
  - In humans, various doses of DAV132, the product formulated for human use

REFERENCES