Estimating an effective dose for a repurposed drug to treat Ebola: the case of favipiravir

France Mentré, Anne-Marie Taburet, Jeremie Guedj, Naïm Bouazza, Jean-Marc Treluyer, Xavier Anglaret, Sakoba Keïta, Xavier de Lamballerie, Pierre Frange, Denis Malvy
Outline

• Introduction
• Dose of favipiravir for patients with EVD
• JIKI Clinical trial
  • Design
  • Implementation
• Modelling PKVK
  • Mouse data
  • Next: NHP
• Lessons learnt
Favipiravir (T-705)

- **Treatment of Ebola Virus Disease**
  - Favipiravir: nucleoside polymerase inhibitor
  - Approved for use in influenza
  - Developed by Toyama Chemicals, Japan
  - Good tolerance
  - Was available in Oct 2014
  - In Ebola infected mice treated with favipiravir: 100% survival (vs 0% untreated)

(Oesterreich et al, Antivir Res, 2014)
Successful treatment of advanced Ebola virus infection with T-705 (favipiravir) in a small animal model

Lisa Oestreich, Anja Lüdtke, Stephanie Wurr, Toni Rieger, César Muñoz-Fontela, Stephan Günther

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*German Centre for Infection Research (DZIF), Partner Site Hamburg, Germany
*Leibniz Institute for Experimental Virology, Martinistrasse 52, 20251 Hamburg, Germany

A

\[
\text{Survival (\%) vs. \text{Log}_{10} \text{conc. (\mu M)}}
\]

- Virus titer (FFU/ml)
- Cell viability

B

95% CI

| IC_{50} | 67 \mu M (10.5 \mu g/ml) |
| IC_{90} | 110 \mu M (17 \mu g/ml) |
| IC_{99} | 186 \mu M (29 \mu g/ml) |

\[
\text{No treatment}
\]

T-705 300 mg/(kg x d) days 6 to 13

n = 10

*** n = 5

T-705 300 mg/(kg x d) days 8 to 14

n.s. n = 5
Evaluation of efficacy and antiviral activity of favipiravir in non-human primates & humans

PI: Hervé Raoul, BSL4, INSERM, France
Enrollment

PROTOCOL

ETHICS

EEUU Grant

Discussions with NGOs

Negociation with pharm. firm

PRE-FIELD PREPARATION

FIELD PREPARATION

7 WEEKS
Dose of favipiravir in EVD adult patients?

• Favipiravir in influenza
  • IC50 of favipiravir 1 µg/ml
  • Protein binding 50%
  • Dosage regimen approved in Japan 1600mg/600mg bid for 4 days
  • Dosage regimen for Phase 3 trial in US 1800mg/800mg bid for 4 days

• Higher studied dose in HV
  • Single dose 2400 mg
  • Maintenance dose 600 mg tid

• Favipiravir in Ebola
  • IC50 of favipiravir 10 µg/ml
  • Mice successfully treated with dose of 150 mg/kg bid per os
  ➢ Dosage regimen in adult patients?
    • IC50 rule: 10 times higher than for influenza = 8 g?
    • Same dose/kg than in mice 150 x 70 = 10.5 g?
Dose of favipiravir in EVD adult patients?

Additional PK data asked to Toyama Chemicals

Toxicokinetics data in mice with same dose

Population PK in Phase 3 US studies
Population PK model (US phase 3 influenza)

\[ \frac{dA_1}{dt} = -A_1 K_a - A_1 V_{max} \cdot A_3 \]

\[ \frac{dA_2}{dt} = A_1 K_a - A_2 V_{max} \cdot A_3 - A_2 K \]

\[ \frac{dA_3}{dt} = K_{deg} \cdot \left[ 1 - \left( \frac{C}{K_M + C} \right) - A_3 \right], A_3^0 = 1 \]
Favipiravir Population Pharmacokinetics Simulation

No.1 1800, 1800/800, 800 mg

Resource data: PopPK simulation

Conc (µg/mL)

Time (hr)
Favipiravir PK in Mice

- Dosing: 150 mg/kg BID per os (H0 and H8)
- Sampling times (D1, D14): H0.5, 1, 3, 8, 8.5, 9, 11, 16, 24
- 108 mice, one sample per mouse
Dose of favipiravir in EVD adult patients (ctd)

- Mice successfully treated with dose of 150 mg/kg bid *per os*
- PK data in mice provided by Toyama

<table>
<thead>
<tr>
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<th>$C_{\text{min}}$ (µg/mL)</th>
<th>$C_{\text{ave}}$ (µg/mL)</th>
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</thead>
<tbody>
<tr>
<td>Free Concentration in mice at steady state</td>
<td>4.5</td>
<td>50</td>
</tr>
<tr>
<td>Corresponding total Concentration in humans at steady state</td>
<td>10</td>
<td>113</td>
</tr>
</tbody>
</table>

- Target exposure in humans found by adjusting on protein binding rate
- Population PK data in patients (US Phase 3 study) obtained from Toyama
  - Simulations of various dosage regimens to achieve target exposure
Favipiravir Population Pharmacokinetics Simulation

No. 3  2400, 2400, 1200/1200, 1200 mg

Resource data: PopPK simulation

African American

Favipiravir pharmacokinetic concentration-time profiles in 100 subjects for dosing scenario was simulated. (Age 35~60 yr, Body weight 60 kg, Race African American)
Dose of favipiravir in EVD adult patients (ctd)

- Maintenance dose: 1200 mg every twelve hours (10 days)
- Need to give a loading dose at **day 1** to rapidly achieve high drug concentration: **2400 mg at H0, 2400 mg at H8, 1200 mg at H16**

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<th>$C_{\text{min}}$ (µg/mL)</th>
<th>$C_{\text{ave}}$ (µg/mL)</th>
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<tbody>
<tr>
<td>Targeted</td>
<td>10</td>
<td>113</td>
</tr>
<tr>
<td>Maintenance dose</td>
<td>57</td>
<td>83.3</td>
</tr>
<tr>
<td>Day 1</td>
<td>9.8 (8 hours)</td>
<td>6.2</td>
</tr>
<tr>
<td></td>
<td>45.2 (16 hours)</td>
<td></td>
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*Mentré et al., Dose regimen of favipiravir for Ebola virus disease, Lancet Infect Dis (2014)*
Favipiravir Dose in children

- Collaboration with JM Treluyer and P Frange (Necker, Paris, France)
- Favipiravir never given in children below 12 years
- Aldehyde oxydase involved in degradation of favipiravir mature at 1 year
- Allometric scaling and use of the PK model to get same exposure than in adults

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>First Day (mg)</th>
<th>2nd to 10th day (mg)</th>
</tr>
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<tbody>
<tr>
<td>10 - 15</td>
<td>600</td>
<td>200</td>
</tr>
<tr>
<td>16 - 21</td>
<td>800</td>
<td>400</td>
</tr>
<tr>
<td>22 - 35</td>
<td>1200</td>
<td>600</td>
</tr>
<tr>
<td>36 - 45</td>
<td>1600</td>
<td>800</td>
</tr>
<tr>
<td>46 - 55</td>
<td>2000</td>
<td>1000</td>
</tr>
<tr>
<td>&gt; 55 (adult)</td>
<td>2400</td>
<td>1200</td>
</tr>
</tbody>
</table>
Simulation in children 10 - 15 kg

Day 1: 600 / 600 / 200
Day 2-10: 200 / 200 / 200

JIKI clinical trial: 
Favipiravir in patients 
with Ebola Virus Disease

(Inserm C1463 - EU H2020 666092)

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Alliance for International Medical Action (ALIMA), France
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Bernhard-Nocht-Institut für Tropenmedizin, Germany
Inserm U1137, Paris Diderot University, France

All authors declared no conflict of interest
The Challenges of Design in Guinea in September 2014

Randomization, while providing the best level of evidence, is not always ethical or possible:

- Ethical arguments should be weighed against the risk/benefit ratio
  - Ebola mortality in Guinea was 60% in adults
  - Favipiravir had an excellent reported safety profile (less than 3% non-severe toxicity)
- RCTs were problematic for the community
  - terrified by the expanding epidemic
  - lacked trust in health-care workers and public authorities
  - informed consent to an RCT was not feasible
Are adaptive randomised trials or non-randomised studies the best way to address the Ebola outbreak in west Africa?

Simone Lanini, Alimuddin Zumla, John P A Ioannidis, Antonino Di Caro, Sanjeev Krishna, Lawrence Gostin, Enrico Girardi, Michel Pletschette, Gino Strada, Aldo Baritussio, Gina Portella, Giovanni Apolone, Silvio Cavuto, Roberto Socoli, Peter Kremsner, Francesco Vairo, Giuseppe Ippolito

Lancet Infect Dis 2015
Published Online
April 14, 2015
http://dx.doi.org/10.1016/S1473-3099(15)00106-4

The Ebola outbreak that has devastated parts of west Africa represents an unprecedented challenge for research and ethics. Estimates from the past three decades emphasise that the present effort to contain the epidemic in the three most affected countries (Guinea, Liberia, and Sierra Leone) has been insufficient, with more than 24,900 cases and about 10,300 deaths, as of March 25, 2015. Faced with such an exceptional event and the urgent response it demands, the use of randomised controlled trials (RCT) for Ebola-related research might be both unethical and infeasible and that potential interventions should be assessed in non-randomised studies on the basis of compassionate use. However, non-randomised studies might not yield valid conclusions, leading to large residual uncertainty about how to interpret the results, and can also waste scarce intervention-related resources, making them profoundly unethical. Scientifically sound and rigorous study designs, such as adaptive RCTs, could provide the best way to reduce the time needed to develop new interventions and to obtain valid results on their efficacy and safety while preserving the application of ethical precepts. We present an overview of clinical studies registered at present at the four main international trial registries and provide a simulation on how adaptive RCTs can behave in this context, when mortality varies simultaneously in either the control or the experimental group.
Evaluating Clinical Trial Designs for Investigational Treatments of Ebola Virus Disease

Ben S. Cooper\textsuperscript{1,2}, Maciej F. Boni\textsuperscript{2,3}, Wirichada Pan-ngum\textsuperscript{4}, Nicholas P. J. Day\textsuperscript{1,2}, Peter W. Horby\textsuperscript{2}, Piero Olliaro\textsuperscript{2,5}, Trudie Lang\textsuperscript{2}, Nicholas J. White\textsuperscript{1,2}, Lisa J. White\textsuperscript{1,2}, John Whitehead\textsuperscript{6}
Design 1. RCT without interim analysis

Design 2. Sequential RCT (up to 20 interim analyses)

Design 3. Multi-stage approach (MSA)

Phase II single-arm study → Phase III Sequential RCT → Roll-out and phase III single-arm confirmation study → continue roll-out

Time to roll-out or rejection
**Objective:** assess efficacy of high-dose favipiravir in decreasing mortality in humans with EVD

**Design:** non-comparative, “proof-of-concept”, phase II trial

**Inclusion criteria:**
- Age >1 year and weight >10 kg, informed consent, able to take oral medications
- Positive EBOV PCR test (RT-PCR, Altona Diagnostics RealStarEbolavirus RT-PCR Kit 1.0)
  → “cycle threshold” ($C_t$) value is inversely proportional to viral load:
  $C_t=20$ equivalent to $10^8$ copies/ml; +3 cycles equivalent to -1 log

**Treatment**
- **Favipiravir**, Toyama Chemical Co., Ltd. Orally administered 200 mg tablets.
- **Adults** (1):
  → Day 0 (inclusion): H0: 2400 mg; H8: 2400 mg; H16: 1200 mg
  → Day 1 to Day 9: 1200 mg bid
- **Children** (2): according to body weight

**JIKI trial protocol**

- **Primary outcome**: mortality at Day 14
- **Secondary outcomes**:
  - Evolution of EBOV plasma RNA and infectious loads
  - Grade 3-4 adverse events
  - EBOV genetic micro-diversity (including resistance mutations)
  - Trough concentrations of favipiravir
- **Analysis**:
  - **Reference**: Pre-trial mortality 55% (MSF/EMLab database, Sept 15- Dec 14, 2015), with same team, same procedures and same laboratory
  - **Stratification variables**: Time since symptom onset: < 72h vs. ≥ 72h
- **Sample size calculation**:
  - Recruitment continues until 60 participants with <72h symptom duration are included (futility analysis every 20 patients)
Settings and teams

• **Funding:**
  – EU/H2020
  – Inserm

• **Partners:**
Inserm, MSF, EuroMobLA, ALIMA, Pasteur, French Red Cross, B-FAST, French Army Health Service

**Settings:** 4 Ebola Treatment Centers:
• 3 in the southern Guinean Highlands (Gueckedou, Nzerekore, Macenta),
• 1 in costal Guinea (Conakry)
Enrollment

- **PROTOCOL**
- **ETHICS**
- **EEUU** Grant
- Discussions with NGOs
- Negotiation with pharm. firm

- **DSMB**
- **TOTAL JIKI**
- **GUECKEDOU/MSF**
- **NZEREKORE/ALIMA**
- **CTS/SSA**
- **MACENTA/Red cross**

- **Enrollment**
- **Pre-Field Preparation**
- **Field Preparation**
- **Trial**

- **6 Weeks**

- **Sept**
- **Oct**
- **Nov**
- **Dec**
- **Jan**
- **Fev**
- **Mar**
- **Apr**
- **May**
Case management center in Gueckedou
High risk zone where confirmed case-patients are hospitalized
Number of cases and deaths among confirmed cases in Guinea


*Documentation non-exhaustive des décès communautaires non-prélévés
RT-PCR CT values at baseline and during follow-up
First 69 adult participants, JIKI trial, 17 DEC 2014 – 20 JAN 2015

<table>
<thead>
<tr>
<th>Adults and children (&gt; 6 yr) with CT ≥ 20</th>
<th>N</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dead</td>
<td>39</td>
<td>6</td>
<td>15.4</td>
</tr>
<tr>
<td>Adults and children (&gt; 6 yr) with CT &lt; 20</td>
<td>28</td>
<td>26</td>
<td>92.9</td>
</tr>
</tbody>
</table>

* 2 patients missing in JIKI for this classification because CT value at inclusion not available
Evaluation of efficacy and antiviral activity of favipiravir in non-human primates & humans
PI: Hervé Raoul, BSL4, INSERM, France
JIKI trial Surveillance

- SAB meetings: Nov 28, Jan 15, Jan 26
- DSMB meetings: Dec 11, Jan 5, Jan 14, Jan 26, April 14

→ On Jan 26, the DSMB approved the investigators’ proposal to make public data from the first 80 participants:
  - No conclusion regarding favipiravir effect on mortality reduction
  - New understanding of EVD pronostic factors that may prove useful to clinicians and researchers developing Ebola treatment protocols

Results presented at CROI, Feb 23-26, 2015, Seattle, Washington

Sissoko et al. Favipiravir in Patients with Ebola Virus Disease: Early Results of the JIKI trial in Guinea, abs. 103-ALB
Modelling PKVK (WP4)
Objectives of Modelling

• To estimate important parameters of the viral lifecycle: infected cell half-life, basic reproductive number
• To estimate the effect of favipiravir in blocking viral production in animal and patients
• To quantify the effect of the immune response
• To investigate the relationship between viremia and survival

• To better understand clinical results and design next studies
Viral dynamics during acute infection

Complex interaction between the pathogen, the drug and the IR

Clearance of infected cell due to:
- immune system
- cytolytic virus
- target cell exhaustion

Viral increase:
- target cell abundance
- large viral burst ($R_0$)
PKVK Model for favipiravir

Pharmacokinetic model based on data in uninfected mice receiving the same dosage regimen

\[ \frac{dT}{dt} = -\beta VT \]
\[ \frac{dI_1}{dt} = \beta VT - kI_1 \]
\[ \frac{dI_2}{dt} = kI_1 - \delta I_2 \]
\[ \frac{dA_c}{dt} = k_a \times A_{dep} - k_e \times A_c \]
\[ C = \frac{A_c}{V} \]
\[ \frac{dC_e}{dt} = k_{e0} \times (C - C_e) \]
\[ \frac{dV}{dt} = \left( 1 - \frac{E_{max} C_e(t)^n}{EC_{50}^n + C_e(t)^n} \right) pI_2 - c_1 V \]
Results: data fitting

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Description</th>
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<tbody>
<tr>
<td>No treatment</td>
<td></td>
</tr>
<tr>
<td>Favi early</td>
<td>Favipiravir 300 mg/kg/day days 6 - 13</td>
</tr>
<tr>
<td>Favi late</td>
<td>Favipiravir 300 mg/kg/day days 8 - 14</td>
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![Graphs showing data fitting for different treatments](image-url)
Results: insights on pathogenesis

• $t_{1/2}$ productively infected cells of 6.4 hours (>10 hours for influenza)
• High steady-state effectiveness of favipiravir in blocking viral production (99.6%)
• A single infected cell could produce ~9 new productive infections (>20 in H1N1 or PR8-PB1-F2(1918))

Modeling strategy
## Lessons learnt for future outbreaks

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<tr>
<th>Science</th>
<th>Infrastructures</th>
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<tr>
<th>Humans</th>
<th>Money</th>
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# Lessons learnt for future outbreaks

<table>
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<tr>
<th>Science</th>
<th>Infrastructures</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Available treatments</td>
<td>• Medical centers</td>
</tr>
<tr>
<td>• Dosage</td>
<td>• Treatment dispensation</td>
</tr>
<tr>
<td>• Study design</td>
<td>• Virological and biological labs</td>
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<table>
<thead>
<tr>
<th>Humans</th>
<th>Money</th>
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<tbody>
<tr>
<td>• Local physicians involved</td>
<td>• Seed money</td>
</tr>
<tr>
<td>• Link with NGO</td>
<td>• Rapid grants</td>
</tr>
<tr>
<td>• Acceptance by population</td>
<td>• Easy transfer</td>
</tr>
<tr>
<td>• Approval by Ethics Committee</td>
<td></td>
</tr>
<tr>
<td>• Clinical research staff</td>
<td></td>
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