In vivo Evaluation of Lassa virus Therapeutics

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Outline:

• Caveats
• Ribavirin
• Favipiravir or Ribavirin
• Favipiravir plus Ribavirin
• Antibody Treatments
• Promising Therapies
• Next Steps
Caveats to testing therapeutics against Lassa virus in animal models

• All the downside of BSL4 environment
  – Safety, limited resources/trained staff, etc.
• Intended routes of administration can be difficult particularly in NHPs
  – i.v, oral, etc.
• Dosage regime
  – Treatments at 8 hours requires large research group
• Immunomodulatory therapeutics
  – If they don’t work are they truly ineffective against the agent, or are they not compatible with the animal?
• Lack of species specific reagents for some models
• Lack of PK data
  – Impede study design
Ribavirin

Synthetic guanosine analogue

Licensed against RSV, Hepatitis C

Administered oral or i.v. routes

Side effects: reversible anemia

Current standard of care for LF

Mechanism of action:
- Lethal mutageneses,
- Direct inhibition of viral polymerase,
- Depletion of intracellular guanosine
Historic Ribavirin data

- Rhesus macaque model
- LASV Josiah ~10e6 pfu
- Two Tx groups n= 4 each, one control group n=10
- Ribavirin: loading dose of 50mg/kg followed by 10mg/kg every 8hrs, s.c.
- 40% survival in controls, 100% survival in treated animals
- Group 0-18: low viremia, mild signs. One went blind ~day 40
- Group 5-18: moderate viremia, moderately severe signs of disease

Stephen & Jarhling 1979; Jarhling et al. 1980

Figure 2. Effect of ribavirin on Lassa fever viremia, given in log_{10} pfu/ml of serum. Groups of four monkeys received ribavirin initially on day 0 (O) or day 5 (●) after inoculation with Lassa virus. Points are geometric mean titers ± se. Curves for lethally infected and surviving controls are those from figure 1.
Favipiravir (T-705)

- **Broad-spectrum antiviral**
  - Pyrazinecarboxamide derivative
- **Active against:**
  - Influenza viruses
  - Flaviviruses (West Nile)
  - Bunyaviruses (La Crosse, Rift Valley)
  - Arenaviruses (Junin)
  - Alphaviruses (Western equine encephalitis virus)
- **Licensed in Japan**
- **Well tolerated in humans**
Ribavirin vs. Favipiravir in Guinea pigs

Day 0
i.p. Challenge 100xLD₅₀ GPA LASV
300-350 g male Hartley strain (n=6-9 group)

Day 42
End of study

Day 2
Once/day, s.c. T-705 or Ribavirin

Day 15
G 1: T-705 300 mg/kg/d
G 2: T-705 150 mg/kg/d
G 3: Ribavirin 50 mg/kg/d
G 4: Placebo

Day p.i.
Survival (%)

A
Tx
T-705, 300 mg/kg/day
T-705, 150 mg/kg/day
Ribavirin, 50 mg/kg/day
Placebo

Day p.i.
% Weight Change

A
Tx
T-705, 300 mg/kg/day
T-705, 150 mg/kg/day
Ribavirin, 50 mg/kg/day
Placebo
Normal
Favipiravir delayed treatments in Guinea pigs
300mg/kg/d T-705

Day 0 to Day 42

i.p. Challenge
100xLD50 GPA - LASV

300-350 g male Hartley strain (n=6 group)
Ribavirin or Favipiravir: NHPs

3x daily s.c treatments (n=4/group)

- Loading dose (i.v.) of 300mg/kg favipiravir or 60 mg/kg ribavirin
- 8 hour treatments (s.c.) of 50mg/kg favipiravir or 10mg/kg ribavirin
- Ribavirin results in delayed disease
- Classic indicators of LF in terminal disease
**Study Design**

- **Day 4**
  - **Tx - s.c., QD, 14 days**
  - **Favipiravir**
  - **Placebo**

- **Day 17**

- **i.m. challenge with 10⁴ TCID₅₀ LASV (strain Josiah)**

- **End of study**
Ribavirin or Favipiravir in mice

- Chimeric, immunocompetent lethal mouse model

- Challenged i.p. with 1000ffu LASV Ba366 (n=5 treated, n=3/7 control)

- Favipiravir: twice daily oral treatments at 75, 150, 300 mg/kg/day from days 4-11

- Ribavirin: i.p. treatments at 80mg/kg once (n=5) or twice (n=5) daily from days 4-11

- Monitored ALT/AST, temp, viremia, tissue titers, body weight

Oestereich et al. 2016
Ribavirin or Favipiravir in mice

Graph showing survival rates and AST levels in mice treated with placebo, Ribavirin 80 mg/kg per day, and Ribavirin 160 mg/kg per day. The graphs compare survival rates and AST levels over different time periods (day 4 to death or days 4–11). The results indicate that Ribavirin at 160 mg/kg per day shows a significant improvement in survival and AST levels compared to the placebo and Ribavirin at 80 mg/kg per day.
Ribavirin + Favipiravir in mice

- Chimeric, immunocompetent lethal mouse model
- Challenged i.p. with 1000ffu LASV Ba366 (n=5 treated, n=3 control)
- Selected sub-optimal doses
  - Ribavirin: Once daily, i.p.
  - 80mg/kg/day on days 4-11
  - 80mg/kg/day on days 4-15
  - 160 mg/kg/day on days 4-11
- All groups received oral Favipiravir twice daily at 150mg/kg/day
- Monitored ALT/AST, temp, viremia, tissue titers, weight
Antibody Treatments

- Hartley outbred lethal Guinea pig model (5-6 weeks old)
- Challenged with 1000 pfu GPA-LASV Josiah
- mAbs given alone or pooled (groups of 2-5) at 30mg/kg on days 0, 3 and 6
- Two control groups: Control was not treated and Hu IgG1 was given an irrelevant mAb
- Monitored clinical score, viremia

Cross, Mire, Branco et al. 2016
ST-193

- Small molecule inhibitor of Lassa virus entry
- Tested in inbred Strain 13 Guinea pigs (6-12 weeks, n=8/group)
- Lethal infection of LASV Josiah
- Once daily i.p. injections for 14 consecutive days beginning 1 hour prior to challenge
- Vehicle, 25mg/kg ST-193, 80 mg/kg ST-193 or 25mg/kg ribavirin
- Monitored blood chems, viremia, histo. path, weight, & temp
- 62.5% of treated animals survived

Cashman et al. 2011