Lassa Fever
Individual Randomize Clinical Trial for Antivirals

Alejandro Costa
Workshop on Efficacy trials for Lassa Fever
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Lassa in Nigeria Epi Week 15

Seasonal transmission in Nigeria with a large outbreak now

- 2017: 143 confirmed cases
- 2018: 416 confirmed cases and 1865 were suspected cases, 1422 were negatives, 105 deaths.
Efficacy of Ribavirin

Very limited evidence.

   a) Efficacy: The data is ambiguous, but suggest that Ribavirin has modest impact on patient survival, only showed effect in patients with ASTs > 150 IU/L
   b) Safety: Non-disease patients treated with Ribavirin had CFR 4 times higher

2. Observational studies and reports. Lack of comparator. No treatment patients were included at the latest state of the disease
Lassa fever – Ascertainment of cases

Confirmed case
Laboratory confirmed (positive IgM antibody, PCR or virus isolation) or epidemiologically linked to a laboratory confirmed case

Suspected case
Illness with gradual onset with one or more of the following: malaise, fever, headache, sore throat, cough, nausea, vomiting, diarrhoea, myalgia, chest pain hearing loss and a history of contact with excreta of rodents or with a suspected /confirmed case of Lassa Fever
Study Description

Multicenter open label individually-randomized treatment study, intend to treat all patients with a laboratory confirmation of Lassa Fever with a 10 day course of IV Ribavirin or oral Favipiravir (or another therapeutic).

The study may also provides post-exposure prophylaxis to high risk population.

The study may take more than one epidemic season
Study design

The study has 4 arms:

a) Treatment with Ribavirin of Lassa confirmed cases
b) Treatment with Favipiravir (or another therapeutic) of Lassa confirmed cases
c) Treatment with Ribavirin and Favipiravir of Lassa confirmed cases
d) Standard supportive care
Individually Randomized Controlled Trial for Ribavirin and Favipiravir or another therapeutic

**Primary objective:**
To determine the efficacy of treatment with Ribavirin for reducing mortality due to confirmed Lassa fever disease

**Secondary objectives:**
To determine the efficacy of treatment with Favipiravir (or another antiviral) or combined Ribavirin and Favipiravir (or another antiviral) for reducing mortality due to confirmed Lassa fever disease
Lassa fever – Therapeutic Trial

Study Population:
Population living in where there is an ongoing outbreak

Treatment effect against Lassa death
1- Primary analysis (factorial design)
Ribavirin vs No Ribavirin

2- Secondary analysis:
Favipiravir vs No Favipiravir
Favipiravir + Ribavirin vs supportive care
Sample size

To achieve 90% power on a two sample test of proportions to detect a reduction in CFR from baseline rate of 20% with a 1:1:1 treatment to control allocation, assuming no loss to follow-up and 20% CFR, and using a Bonferroni correction for more of one antiviral to account for multiple comparisons. Uses alpha=0.05 for each primary analysis.

<table>
<thead>
<tr>
<th>Therapeutic effect</th>
<th>Crude sample size in each arm</th>
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<tbody>
<tr>
<td>10%</td>
<td>9549</td>
</tr>
<tr>
<td>20%</td>
<td>2288</td>
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<tr>
<td>30%</td>
<td>971</td>
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<td>50%</td>
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<td>70%</td>
<td>141</td>
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<td>80%</td>
<td>101</td>
</tr>
<tr>
<td>90%</td>
<td>73</td>
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</tbody>
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Inclusion criteria

• All patients that meets the Case definition for LF confirmed case
• > 6 years of age
• Agrees to collection of required specimens
• Agrees to report any Adverse Events, Serious and Unexpected Adverse Events for the duration of the study
Exclusion criteria

- Known intolerance to Ribavirin or Favipiravir.
- Is irreversibly ill on presentation.
- History of hemoglobinopathies (i.e., sickle-cell anemia or thalassemia major). Hemoglobin less than 10 g/dL before initiation of IV Ribavirin.
- Creatinine clearance of < 30 mL/min.
- Pregnant women.
- Children < 6 year old.
Treatment and dosage

Ribavirin: Tablets 200 mg COPEGUS® (Hoffmann La Roche) and liquid IV presentation 2 ml ampules (Grand Pharmaceutical) and VIRAZOLE® (Legacy Pharmaceuticals/MEDA Pharma, Mylan) 12 ml vials

- IV administration: loading dose 30 mg/kg (max per dose), day 1-4 = 17 mg/kg every 6 hours (max 1000 mg per dose), day 5-10 = 8 mg/kg every 8 hours (max 500 mg per dose).
- Oral Ribavirin: loading dose 2000 mg, day 1-5 = 1000 mg every 6 hours and day 5-10 = 500 mg every 6 hours
Favipiravir  brand name: AVIGAN® Tablet 200mg (Toyama Chemical/ FUJIFILM).

Oral administration: based on Jiki trial Ebola: loading dose 6000 mg, day 1-9 = 2400 mg/day
Discussion

1. Agreement on individual randomized clinical trial, multi-center, multi-country
2. Agreement to test Ribavirin efficacy
3. Another antiviral?, Favipiravir?
4. Primary outcome to reduce CRF by 50 %, 70 %?
5. Secondary outcomes: severity of the disease, viremia, etc
6. Inclusion and exclusion criteria: children and pregnant women
7. Duration of the treatment, 10 days
8. Accumulative data across different trials
9. Post-exposure prophylaxis (e.g. oral ribavirin, oral favipiravir, other PEP antivirals easy to administer)
Thank you