Lassa treatment evaluation

WHO R&D Blueprint
5th consultation on clinical trial designs
29 November 2018, Geneva, Switzerland
Overview of study design options being proposed for implementation

• Scientific perspectives

• Ethical challenges

• Statistical considerations

• Implementation challenges
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1. Estimated 37.7 million people in 14 countries at risk of infection.  

2. Estimated 100,000-300,000 cases and 5000 deaths annually.

3. Case fatality ratio (CFR) in hospitalised patients ranges from 15-20%.  

4. Higher rates reported.

5. Recent outbreak in Nigeria CFR 25.4%

Lassa fever therapeutics

• There are no licensed therapeutics for Lassa

• Ribavirin widely used ‘off-label’ since 1978

• Various dosing regimens

• Expensive (>USD1000)

• Difficult to source

• Efficacy?
Source: WHO Konstantin Volkmann.
No randomized efficacy data was identified, only one clinical trial but it was analysed as an observational study.  

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Lived</th>
<th>Died</th>
<th>% cases fatal</th>
</tr>
</thead>
<tbody>
<tr>
<td>No therapy</td>
<td>27</td>
<td>33</td>
<td>55</td>
</tr>
<tr>
<td>IV ribavirin</td>
<td>51</td>
<td>12</td>
<td>19</td>
</tr>
</tbody>
</table>

$p < 0.001$

**But:**
- In patients with AST < 150 IU/L CFR appeared higher in ribavirin treated group
- Undiagnosed patients: In ribavirin treated CFR 4 times higher than untreated
- And critical risk of bias
  - *Historic controls*
  - *Post-hoc grouping of subjects based on CFR*
  - *Small numbers (underpowered)*
ddC/ddI - rate of Progression to AIDS/Death

8/29/91 (39/19)  
\[ 2.08 \quad 1.25 \quad 0.88 \]

11/7/91 (66/50)  
\[ 2.44 \quad 2.04 \quad 1.41 \quad 1.00 \quad 0.82 \]

2/13/92 (91/77)  
\[ 1.75 \quad 1.64 \quad 1.20 \quad 0.89 \quad 0.82 \]

8/21/92 (130/130)  
\[ 1.25 \quad 1.00 \quad 0.80 \]

* Had 39 vs 19 data been released ⇒ Pre-judgment

Why Most Published Research Findings Are False
Ioannidis (2005)

Table 4. PPV of Research Findings for Various Combinations of Power (1 - β), Ratio of True to Not-True Relationships (R), and Bias (u)

<table>
<thead>
<tr>
<th>$1 - \beta$</th>
<th>$R$</th>
<th>$u$</th>
<th>Practical Example</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.80</td>
<td>1:1</td>
<td>0.10</td>
<td>Adequately powered RCT with little bias and 1:1 pre-study odds</td>
<td>0.85</td>
</tr>
<tr>
<td>0.95</td>
<td>2:1</td>
<td>0.30</td>
<td>Confirmatory meta-analysis of good-quality RCTs</td>
<td>0.85</td>
</tr>
<tr>
<td>0.80</td>
<td>1:3</td>
<td>0.40</td>
<td>Meta-analysis of small inconclusive studies</td>
<td>0.41</td>
</tr>
<tr>
<td>0.20</td>
<td>1:5</td>
<td>0.20</td>
<td>Underpowered, but well-performed phase I/II RCT</td>
<td>0.23</td>
</tr>
<tr>
<td>0.20</td>
<td>1:5</td>
<td>0.80</td>
<td>Underpowered, poorly performed phase I/II RCT</td>
<td>0.17</td>
</tr>
<tr>
<td>0.80</td>
<td>1:10</td>
<td>0.30</td>
<td>Adequately powered exploratory epidemiological study</td>
<td>0.20</td>
</tr>
<tr>
<td>0.20</td>
<td>1:10</td>
<td>0.30</td>
<td>Underpowered exploratory epidemiological study</td>
<td>0.12</td>
</tr>
<tr>
<td>0.20</td>
<td>1:1,000</td>
<td>0.80</td>
<td>Discovery-oriented exploratory research with massive testing</td>
<td>0.0010</td>
</tr>
<tr>
<td>0.20</td>
<td>1:1,000</td>
<td>0.20</td>
<td>As in previous example, but with more limited bias (more standardized)</td>
<td>0.0015</td>
</tr>
</tbody>
</table>

Clinical trial success rates 13.8 %
Biostatistics (2018) pp. 1–14
10%
Nature Biotechnology 32, 40–51.
Data on ribavirin efficacy and safety are inconclusive

• Is it helping or harming? → duty of care now

• Not licensable

• Not an acceptable comparator for clinical trials (superior, equal or inferior to what?)

• There are at least 12 therapeutic candidates in pipeline

• Without definitive evidence of ribavirin efficacy we cannot properly evaluate any new therapeutics

• Perpetual uncertainty

• Care for Lassa patients will not improve
We need unbiased evidence

CAST (Cardiac Arrhythmias Suppression Trial)
• Early 1980’s new antiarrhythmics found to be highly successful at suppressing arrhythmias
• Not until an RCT was done was it shown that arrhythmias were controlled, but mortality increased
• Excess mortality of 56/1000
• By time RCT was published > 100,000 patients given the drugs

FEAST (Fluid Expansion As Supportive Therapy)
• Fluid boluses significantly increased 48-hour mortality in critically ill children with impaired perfusion

What to do?
Example - oseltamivir

- Not licensed for severe influenza, no RCT data
- Widely used as standard of care
- Conclusion: There were no virological or clinical advantages with double dose oseltamivir compared with standard dose.

➤ Both work equally well?
➤ Both do nothing?
➤ Both equally harmful?

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*The News About Tamiflu: It Doesn't Work*

*Posted: 12/09/2013 12:01 pm EST  |  Updated: 02/08/2014 5:59 am EST*
• Given the weaknesses in the current evidence base, the steering group considers that it is essential to conduct new high-quality and adequately powered RCTs to address key uncertainties.
To remove uncertainty – we need an RCT

WHO Workshop April 25th 2018, Paris
Efficacy trials of Lassa Therapeutics: endpoints, trial design, site selection

“the need to generate randomized evidence on ribavirin efficacy has strong implication on a Phase 2b/3 trial design and notably implies the definition of a trial comparator group whereby participants would be randomly allocated to receive the best supportive care without ribavirin.”

Proposal: A multicentre, individually-randomized, two-arm, placebo-controlled trial comparing ribavirin plus optimized standard of care (oSOC) versus oSOC with placebo.

1. True equipoise
2. Greatest scientific validity
3. Greatest social value
| Précis | A multicentre, individually-randomized, two-arm, placebo-controlled trial comparing ribavirin plus optimized standard of care (oSOC) versus oSOC with placebo for the reduction of mortality in hospitalised patients with laboratory-confirmed Lassa fever. |
| Primary objective | To evaluate whether intravenous ribavirin *<insert dose>* improves survival in patients with confirmed Lassa fever compared to placebo. |
| Primary endpoint | Mortality [Time frame: 28 days after randomisation] |
| Secondary objectives | To evaluate the safety of intravenous ribavirin *<insert dose>* in patients with confirmed Lassa fever compared to placebo.  
To evaluate whether intravenous ribavirin reduces viral load in patients with confirmed Lassa fever compared to placebo. |
| Secondary endpoints | Frequency of serious adverse events [Time frame: 28 days after randomisation]  
Time to undetectable viral load by PCR [Time frame: right censored by day of death or discharge]  
Area under the curve (AUC) viral load [Time frame: right censored by day of death or discharge] |
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Ethical challenges

• Placebo or no-ribavirin arm
  • “Where no proven intervention exists, the use of placebo,
    or no intervention, is acceptable.” Declaration of Helsinki

• Community acceptance

• Treatment options for people who decline to participate in trial

• Those with known conditions for which ribavirin is contraindicated e.g. pregnant women, hemoglobinopathies, unstable cardiac disease
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Primary statistical analysis

- Null hypothesis would be that ribavirin has no effect on 28-day mortality.
- Analysis conducted according to the intention-to-treat principle.
- The primary analysis conducted using a chi-square test of independence for the 2x2 table of trial arm versus 28-day mortality.
- The analysis will be two-sided with type 1 error set at 0.05.

<table>
<thead>
<tr>
<th></th>
<th>Ribavirin + OSOC</th>
<th>OSOC</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Died</td>
<td>A</td>
<td>C</td>
<td>$S_1$</td>
</tr>
<tr>
<td>Survived</td>
<td>B</td>
<td>D</td>
<td>$S_2$</td>
</tr>
<tr>
<td>Total</td>
<td>$N_1$</td>
<td>$N_2$</td>
<td>$T$</td>
</tr>
</tbody>
</table>

$$\text{Chi squared} = \frac{T(AD-BC)^2}{N_1N_2S_1S_2}$$
Crude sample size estimates

Based on:

One-sided $\alpha = 0.025$
Power = 0.80
Initial design assumption (CFR 20%, efficacy = 50%)

<table>
<thead>
<tr>
<th>oSOC + placebo CFR</th>
<th>Ribavirin efficacy</th>
<th>Rib + oSOC CFR</th>
<th>Sample size (cases) per arm</th>
<th>Total sample size</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.10</td>
<td>30%</td>
<td>0.070</td>
<td>1,356</td>
<td>2,712</td>
</tr>
<tr>
<td></td>
<td>50%</td>
<td>0.050</td>
<td>435</td>
<td>870</td>
</tr>
<tr>
<td>0.15</td>
<td>30%</td>
<td>0.105</td>
<td>864</td>
<td>1,724</td>
</tr>
<tr>
<td></td>
<td>50%</td>
<td>0.075</td>
<td>278</td>
<td>556</td>
</tr>
<tr>
<td>0.20</td>
<td>30%</td>
<td>0.140</td>
<td>615</td>
<td>1,230</td>
</tr>
<tr>
<td></td>
<td>50%</td>
<td>0.100</td>
<td>199</td>
<td>398 (red border)</td>
</tr>
<tr>
<td>0.25</td>
<td>30%</td>
<td>0.175</td>
<td>464</td>
<td>928</td>
</tr>
<tr>
<td></td>
<td>50%</td>
<td>0.125</td>
<td>150</td>
<td>300</td>
</tr>
</tbody>
</table>
Interim and secondary analyses

• Annual blinded interim analysis by DSMB for efficacy and futility.

• A planned sample size review at interim analysis based on blinded, aggregated CFR across both groups.

• Interim analyses will inflate sample size (5-10%) 

• Secondary stratified analysis of CFR by:
  • Time from symptom onset to treatment (*perhaps binary* ≤ 6 vs > 6 days)
  • Baseline CT value
  • AST/SGOT < 150 vs. ≥150
RANDOMIZATION

• Eligible cases to be individually randomized using block randomization with randomly varying block lengths.

• Randomization will be stratified by site.

To balance treatment allocation between sites and reduce confounding by inter-site heterogeneity in CFR.
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Implementation challenges

• Ribavirin dose
  • Varying doses and schedules in use
  • Very little pharmacokinetic or pharmacodynamic data
  • Mechanism of action uncertain

• Standard of care
  • Renal replacement therapy?
  • Blood coagulation screens / inotropes / renal replacement therapy / mechanical ventilation?

• Different Lassa virus strains (different severity?)
Time for a landmark trial – set the benchmark

• Trial conception ✓
• Trial design and planning
  • Assemble study team
  • Finalise protocol & other study documentation
• Trial agreements
  • Identify sponsor & secure insurance
  • Secure funding
  • Prepare clinical trial agreements
• Trial approval
  • Obtain ethical and regulatory approval
• Trial set-up
Thank you for your attention
Eligibility

Inclusion criteria

• Admitted to hospital
• Age at least 1 year of age
• Laboratory confirmed Lassa fever infection (RT-PCR, using a combination of two quantitative PCRs performed by a designated laboratory).
• Informed consent. Parental consent/child assent for child participation.
• All women will be eligible regardless of pregnancy status if, after counselling regarding the risks/benefits of treatment, they consent.

Exclusion Criteria

• Known intolerance to ribavirin
• Hemoglobinopathies (i.e. sickle-cell anemia or thalassemia major)
• Hb < 8g/dL
• Estimated creatinine clearance <30ml/min
• **Nigeria**
  - Loading dose 33 mg/kg (maximum 2.64 g)
  - Day 1-4 16 mg/kg (maximum 1.28 g per dose) intravenously QDS [four days]
  - Day 5-10 8 mg/kg intravenously (maximum 640 mg per dose) TD [six days].

• **Sierra Leone**
  - Loading dose 30 mg/kg (maximum 2 g)
  - Day 1-4 15 mg/kg (maximum 1 g per dose) intravenously QDS [four days]
  - Day 5-10 7.5 mg/kg intravenously (maximum 500 mg per dose) TDS [six days]

• **WHO [adults and children]**
  - Loading dose 30mg/kg (maximum 2g)
  - Day 1-4 15 mg/kg (maximum 1g per dose) q 6h [four days]
  - Day 5-10 7.5 mg/kg (maximum 500mg per dose) q 8h [six days]

• Nigeria CDC Standard operating procedures for Lassa fever case management
• WHO Clinical management of patients with viral haemorrhagic fever: a pocket guide for front line health workers. Feb 2016
Assessed for eligibility

Excluded (n= )
- Not meeting inclusion criteria (n= )
- Declined (n= )
- Other reason (n= )

Randomised (n= )

Allocated to ribavirin + oSoC (n= )
- Received allocated intervention (n= )
- Did not receive allocated intervention (n= )

Lost to follow up (n= )
Discontinued intervention (n= )

Analysed (n= )
- Excluded from analysis (n= )

Allocated to placebo + oSoC (n= )
- Received allocated intervention (n= )
- Did not receive allocated intervention (n= )

Lost to follow up (n= )
Discontinued intervention (n= )

Analysed (n= )
- Excluded from analysis (n= )
<table>
<thead>
<tr>
<th>Variables</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Symptoms and signs</td>
<td>X X X X X X X X X X X</td>
</tr>
<tr>
<td>Vital signs</td>
<td>X X X X X X X X X X X</td>
</tr>
<tr>
<td>Malaria RDT</td>
<td>X</td>
</tr>
<tr>
<td>Urine - βHCG (females of child bearing age)</td>
<td>X</td>
</tr>
<tr>
<td>Finger prick - random glucose</td>
<td>X</td>
</tr>
<tr>
<td>Blood - EDTA - viral load, FBC, haematocrit, lactate</td>
<td>X X X X X X X X X X X</td>
</tr>
<tr>
<td></td>
<td>(5mL - adult)</td>
</tr>
<tr>
<td>Blood - serum separator tube - liver function test, electrolytes, urea, creatinine, save serum</td>
<td>X X X X X X X X X X</td>
</tr>
<tr>
<td></td>
<td>(5mL - adult)</td>
</tr>
<tr>
<td>Serious adverse events monitoring</td>
<td>X X X X X X X X X X X X</td>
</tr>
<tr>
<td>Outcome</td>
<td>X X X X X X X X X X X X</td>
</tr>
</tbody>
</table>

Lassa therapeutic evaluation – November 2018
Statistical analysis

• Blinded interim analysis by DSMB annually for efficacy and futility.

• Master protocol – pre-plan to keep data blinded until answer is reached.

• Build in flexibility - ? CFR, ordinal scale [discharged, hospitalized, dead], odds ratio rather than fixed effect

• GOST – “An advantage of the approach is that any erroneous assumptions made at the design stage about the proportion of patients falling into each outcome category have little effect on the error probabilities of the study, although they can lead to inaccurate forecasts of sample size.”

• Builds in simplicity – robust to heterogeneity