Ribavirin efficacy in Lassa fever
Preliminary results from a systematic literature review

Workshop on Efficacy trials for Lassa Fever
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Ribavirin

• Nucleoside analogue agent
• It is licensed for hepatitis C virus and used off-label to treat RNA hemorrhagic fevers
• Side effects include headache, abdominal cramps, fatigue, reversible anaemia and elevation of bilirubin concentrations\(^1\)
• Approximate cost for patient to complete the Lassa regime varies, with an average of 5000 EUR\(^2\)

1) Cameo Chemicals
Systematic review approach

Aim

- To examine publically available evidence related to treatment efficacy of ribavirin in Lassa fever (no grey or unpublished data)
- To contribute to the discussion about RCT design testing efficacy and future standard of care

Search Criteria

- Keywords: “Lassa fever”, “virus”, “infection”, “therapy”, ”ribavirin”
- Databases: PubMed and the Cochrane Library

((("lassa fever"[MeSH Terms] OR "lassa"[All Fields] AND "fever"[All Fields]) OR "lassa fever"[All Fields]) AND ("infection"[MeSH Terms] OR "infection"[All Fields])) AND ("viruses"[MeSH Terms] OR "viruses"[All Fields] OR "virus"[All Fields])) AND ("therapy"[Subheading] OR "therapy"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields])) AND ("ribavirin"[MeSH Terms] OR "ribavirin"[All Fields])
A framework for assessing evidence from the systematic review

Robins-I

- Risk of bias assessment for non-randomised studies (1)
- Low -> Medium -> Serious -> Critical risk of bias
- Overall confounding domains: criteria for ribavirin treatment and patient profile at beginning of ribavirin treatment

Comparative assessment of literature results

- Comparing effects across the literature using forest plots with confidence intervals (2)
- Heterogeneity in the literature was assessed using $Q$ tests and $I^2$-squared values

$$Q = \sum w \, ES^2 - \frac{[\sum (w \, ES)]^2}{\sum w}$$

$$I^2 = \frac{(Q - df)}{Q}$$

$$CI = p \pm \frac{z}{1 + \frac{z^2}{N}} \sqrt{\frac{p (1 - p)}{N} + \frac{z^2}{4 N^2}}$$


Records identified through database searching (n=31)

Records after duplicates removed (n=33)

Records screened (n=33)

Records excluded due to full-text unavailability (n=1)

Full-text articles assessed for eligibility (n=32)

Articles included in the review (n=12)
  • 1 clinical trial

Articles reporting treatment vs. no treatment groups (n=5)

Full-text articles excluded, with reasons (n=21)
  • Relevance
  • Ribavirin not in methods and results
  • Animal models only

Full-text article that intentionally withheld ribavirin in methods (n=1)
Measured outcomes

- Case fatality rate (CFR)
  \[ cfr = \frac{N_{\text{fatalities}}}{N_{\text{sample}}} \]

- Ribavirin treatment
- No treatment
Overall studies (n=12)

- Studies (n=6) assessing effect on evacuated/imported cases
  Fatal cases = 0

- Studies (n=6) reporting cases in endemic areas
  Articles (n=6)
  Fatal cases > 0

  - 4 studies with comparative groups
  - 2 studies with ribavirin only
  - 1 RCT
Studies that reported no fatalities

<table>
<thead>
<tr>
<th>Study</th>
<th>No ribavirin</th>
<th>Ribavirin</th>
<th>Risk of bias (Robins –I)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lab Confirmed</td>
<td>Suspected</td>
<td>Lab Confirmed</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
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<td>3</td>
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<tr>
<td>6</td>
<td>0</td>
<td>0</td>
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</tr>
</tbody>
</table>

Critical risk of bias: “The study is too problematic to provide any useful evidence on the effects of intervention.”
Study presentation structure

Overall studies (n=12)

- Articles observing imported cases (n=6)
  - Fatal cases = 0

- Articles observing cases in endemic areas articles (n=6)
  - Fatal cases > 0
    - 4 articles with comparative groups
    - 2 articles with ribavirin only
    - 1 RCT
Reported case fatality rates from trial that was analysed as an observational study (McCormick et al., 1986)

**Elev. TCID, 6 days**
- No therapy: 30% (10,50), N=20
- Plasma: 56% (23,88), N=9
- IV ribavirin: 9% (0,26), N=11
- Oral ribavirin: 20% (0,55), N=5

**Elev. AST, 6 days**
- No therapy: 61% (39,84), N=18
- Plasma: 38% (14,61), N=16
- IV ribavirin: 5% (0,15), N=20
- Oral ribavirin: 20% (0,55), N=5

**Elev. TCID, 7 days**
- No therapy: 78% (62,93), N=27
- Plasma: 58% (30,86), N=12
- IV ribavirin: 47% (25,70), N=19
- Oral ribavirin: 40% (0,83), N=5

**Elev. AST, 7 days**
- No therapy: 52% (37,67), N=42
- Plasma: 92% (77,100), N=12
- IV ribavirin: 26% (13,39), N=43
- Oral ribavirin: 11% (0,32), N=9

AST=aspartate Aminotransferase, elevated here means > 150 IU/l
TCID$_{50}$=tissue culture infection dose, elevated here means serum virus levels >10
Trial analysed as an observational study
Retrospective grouping based on CFR results

- Plasma (1 unit) 9/31
- Plasma (2 units) 8/22
- IV ribavirin 6/30
- *Plasma + IV rib. 7/32

N= 53

N= 62

* Differences were determined not to be significant in therapeutic effect from plasma alone, therefore these patients were combined into a single group treated with IV ribavirin.

Table 2: Outcome of LF in patients admitted with Serum Virus levels \( \geq 10^{3.6} \) TCID\textsubscript{50} per millilitre

<table>
<thead>
<tr>
<th></th>
<th>lived</th>
<th>died</th>
<th>lived</th>
<th>died</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV rib</td>
<td>21</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma</td>
<td>9</td>
<td>12</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3: Outcome of LF in patients admitted with AST \( >150 \) IU per litre

<table>
<thead>
<tr>
<th></th>
<th>Tx within 6 days</th>
<th>Tx at 7 days or later</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV rib</td>
<td>19</td>
<td>1</td>
</tr>
<tr>
<td>Plasma</td>
<td>10</td>
<td>6</td>
</tr>
</tbody>
</table>

Table 4: Outcome of LF in patients admitted with Serum Virus levels \( \geq 10^{3.6} \) TCID\textsubscript{50} per millilitre

<table>
<thead>
<tr>
<th></th>
<th>Tx within 6 days</th>
<th>Tx at 7 days or later</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV rib</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Plasma</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

Table 5: Outcome of LF in patients admitted with Serum Virus levels \( <10^{3.6} \) TCID\textsubscript{50} per millilitre

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>IV rib</td>
<td>29</td>
</tr>
<tr>
<td>Plasma</td>
<td>27</td>
</tr>
</tbody>
</table>
Clinical trial analysed as observational study: Risk of bias

• Not randomised: “…we eventually did not use randomized untreated patients, but rather a retrospective untreated comparison group.”

• Serious risk of bias (ROBINS-I)

• In the only clinical trial, there was deviation from planned research protocol. Unclear retrospective cohort grouping (how many cases are actually included, how groups are merged, total sample size is missing)

• Unclear how groups were selected for comparison (plasma vs. ribavirin vs. no treatment) and if selected prior to the study begin or afterwards
Reported CFRs following Ribavirin administration – All studies are afflicted by critical risk of bias

McCormick, 1986
No therapy 56%(45,65), N=107
Ribavirin 24%(12,27), N=93

Shaffer, 2014
No therapy 92%(34,100), N=13
Ribavirin 44%(26,63), N=27

Dahnmane, 2014
No therapy 54%(42,67), N=64
Ribavirin 40%(19,61), N=20

Ajayi, 2013
No therapy 100%(25,100), N=4
Ribavirin 13%(0,29), N=16

Okokhere, 2018
Ribavirin 24%(19,29), N=284

Inegbenebor, 2010
Ribavirin 28%(18,39), N=64

Due to the methods used in these studies we cannot extract results that are free from bias with regards to ribavirin efficacy (not designed to test efficacy)
What is the criterion to include a patient into a treatment or no treatment group?

-> Problematic when decided retrospectively

Estimated CFRs: adjusting for outcome-related selectivity (i.e. excluding those who died without any form of treatment)
Reported CRF according to time from onset to administration of Ribavirin

**Treatment > 6 days**
- Ribavirin: 87% (41,1), n=16
- Ribavirin: 75% (14,1), n=8
- No therapy: 45% (25,64), n=47
- No therapy: 52% (30,74), n=42
- Ribavirin: 35% (14,54), n=32
- Ribavirin: 47% (16,78), n=19
- Conv. plasma: 59% (15,1), n=12
- Conv. plasma: 67% (20,1), n=12
- Oral ribavirin: 40% (0,90), n=5
- Oral ribavirin: 12% (0,32), n=9

**Treatment < 6 days**
- Ribavirin: 11% (0,30), n=16
- Ribavirin: 25% (0,60), n=8
- Oral ribavirin: 5% (0,36), n=2
- No therapy: 15% (3,28), n=38
- No therapy: 28% (12,46), n=38
- Ribavirin: 9% (0,26), n=11
- Ribavirin: 5% (0,14), n=20
- Ribavirin: 2% (2,37), n=25
- Conv. plasma: 24% (5,43), n=25
- Conv. plasma: 20% (0,59), n=5
- Oral ribavirin: 20% (0,59), n=5
Additional factors that limit comparability across studies

- Variability in dosages (reported in 33% of studies)

<table>
<thead>
<tr>
<th>Dosage and regimen</th>
<th>N articles reporting</th>
</tr>
</thead>
<tbody>
<tr>
<td>10mg/ kg, 4x day, 5-8 days</td>
<td>1</td>
</tr>
<tr>
<td>100mg/kg divided dosage on day1, 25 mg/kg daily (days 2-6), 12.5 mg/kg daily (days 7-10)</td>
<td>1</td>
</tr>
<tr>
<td>600mg, 4x day, 10 days</td>
<td>2</td>
</tr>
<tr>
<td>1x 30mg/kg, 15mg/kg, 4x day for first 4 days, 7.5 mg/kg 3x day for last 6 days (intravenous)</td>
<td>1</td>
</tr>
<tr>
<td>400 mg 4x day, 10 days (children)</td>
<td>1</td>
</tr>
<tr>
<td>2g single dose, followed by 1g 3x day, 1-8 days (oral), 16mg/kg, 4x day, 9-12 days, 8mmg/kg 3xday, 13-15 days</td>
<td>1</td>
</tr>
<tr>
<td>2g single dose, 1 g 4x day, 4 days, 500mg 3x day 5-10)</td>
<td>1</td>
</tr>
<tr>
<td>Dosage not specified</td>
<td>4</td>
</tr>
</tbody>
</table>
Additional factors that limit comparability across articles

• Variations in supportive care provided
  – Articles reporting retrospective analyses were unable to control the standard of care across multiple sites
  – One article explicitly reports haemodialysis (CFR reduction from 70% to 56%, but no control)

• Different strains of Lassa across different sites in Africa

• Variations in time between onset of symptoms and initiation of treatment

• Case definitions/ inclusion criteria for treatment
  – Denominator in CFR calculations
  – Most articles included cases who show epidemiological signs of Lassa
  – Some articles use PCR (but not consistently and not for all cases)
  – It remains generally unclear what factors (besides early death) decided administration of ribavirin vs. no treatment
Preliminary conclusions

• **No** randomized efficacy data was identified, only one clinical trial but it was analysed as an observational study.

• All observational studies have critical risk of bias regarding evidence for ribavirin efficacy
Preliminary conclusions

• Data suggest lower CFRs for treatment groups compared to no-treatment groups however confounders and risk of bias limit the interpretation of those data.

• In some studies, patients were too ill to benefit from treatment and often were counted as deaths in the no treatment group

• Data suggest that time to start treatment AND supportive care seems to have an impact on CFR (e.g: after 6 days = higher CFRs are reported)
Thank You
Clinical trial represents a key reference

Clinical trial (McCormick et al., 1986)

Observational (Haas et al., 2003)
Observational (Ajayi et al., 2013)
Observational (Inegbenebor et al., 2010)
Observational (Crowcroft et al., 2004)
Observational (Dahmane et al., 2014)
Observational (Rasbe et al., 2017)
Observational (Raabe et al., 2017)
Observational (Okokhere et al., 2018)
Observational (Amorosa et al., 2010)
Observational (Ehlkes et al., 2016)
## Equation list

<table>
<thead>
<tr>
<th>Key equations used</th>
<th>Effect size (outcome)</th>
<th>Variance of studies</th>
<th>Study weights (inverse of its variance)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Q test for heterogeneity</strong></td>
<td>$Q = \sum w \cdot ES^2 - \frac{[\sum (w \cdot ES)]^2}{\sum w}$</td>
<td>$ES = \frac{\text{events}}{\text{sample size}}$</td>
<td>$w = \frac{1}{\text{var}^2}$</td>
</tr>
<tr>
<td><strong>I² quantifying heterogeneity between studies</strong></td>
<td>$I^2 = \frac{(Q - df)}{Q}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>95% confidence interval for CFRs</strong></td>
<td>$CI = ES \pm 1.96 \sqrt{\frac{ES (1 - ES)}{\text{sample size}}}$</td>
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</tr>
</tbody>
</table>
Overall CFRs bias reports

Clinical trial (1986)
- No therapy 56%(45,65), N=107
- Ribavirin 24%(12,27), N=93

Report l (Shaffer, 2014)
- No therapy 92%(77,100), N=13
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Report (Okokhere, 2018)
- Ribavirin 24%(19,29), N=284

Report (Inegbenebor, 2010)
- Ribavirin 28%(18,39), N=64

- Critical risk (Robins – I)
- Cohort selected from a larger study
- Outcome not always known (only blood sample and treatment data available)

- Critical risk (Robins – I)
- Treatment selection based on knowledge of outcome (pre-treatment fatalities)
- Missing data only in one intervention group

- Critical risk (Robins – I)
- Treatment selection based on knowledge of outcome (pre-treatment fatalities)
- Cohort selected from a larger study

- Low risk (Robins – I)
- No control group

- Medium risk (Robins – I)
- Cohort selected from larger study
- No information on study inclusion criteria
- No control group