WHO R&D Blueprint

Conclusions from Lassa Fever R&D roadmap

Therapeutics

Efficacy Trials of Lassa Therapeutics

endpoints, trial design, site selection

Workshop, Paris 25 April 2018

Marie-Pierre Preziosi, MD PhD
AN R&D BLUEPRINT FOR ACTION TO PREVENT EPIDEMICS

PLAN OF ACTION

MAY 2016

World Health Organization
The R&D Blueprint: how it works

Prioritization Process → Priority list of Pathogens → R&D Roadmaps → Target Product Profiles

Development of Products

Clinical Trial Design → Regulatory pathways; EUAL

SAG
Scientific Advisory Group

GCM
Global Coordination Mechanism

M&E
Monitoring & Evaluation

Data & Sample sharing

Lassa workshop, 25 April 2018
Vision

Robust medical countermeasures to detect, control, and prevent Lassa fever that are readily available and accessible for use in at-risk areas for both endemic and outbreak-related disease.

These medical countermeasures include:
- Rapid, accurate, point-of-care diagnostics for Lassa fever
- Safe and effective treatment and post-exposure prophylaxis for Lassa fever
- Safe and effective vaccines to prevent disease, disability, and death from Lassa fever and stop person-to-person transmission of Lassa virus.
Therapeutic interventions

No specific antiviral therapy approved for use in the treatment of Lassa Fever

Therapeutic options most widely used limited to

- General supportive measures
- Off-label use of the antiviral ribavirin
Antiviral drugs

No experimental antiviral drug yet tested in Lassa Fever patients or Non-Human Primate model

Several candidates associated with antiviral activity in vitro

– targeting either virus entry or
– later stages of the viral replication cycle

A few of them also showed efficacy in small animal models
## Antiviral candidates considered

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Efficacy</th>
<th>Animal Model</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Favipiravir</strong> (or T-705, nucleoside analogue)</td>
<td>100% (300 mg/kg/d, x14 d), even with treatment starting on day 7</td>
<td>Guinea Pigs (intraperitoneal challenge with Josiah strain)</td>
<td>Safronez 2015</td>
</tr>
<tr>
<td><strong>Zidampidine</strong> (nucleoside analogue, an aryl phosphate derivative of AZT)</td>
<td>100% (25 mg/kg, 6 doses administered 24 h prior, 1 h prior, and 24, 48, 72, and 96 h after challenge)</td>
<td>CBA Mice (intracranial challenge with Josiah strain)</td>
<td>Uckun 2005</td>
</tr>
<tr>
<td><strong>Stampidine</strong> (derivative of stavudine)</td>
<td>75% (25 mg/kg) and 90% (50 mg/kg)</td>
<td>CBA Mice (intracranial challenge with Josiah strain)</td>
<td>Uckun 2004</td>
</tr>
<tr>
<td><strong>ST-193</strong> (small-molecule entry inhibitor)</td>
<td>62.5% (25 mg/kg and 80 mg/kg/d, x14 d, starting 1 h before challenge)</td>
<td>Guinea Pigs (subcutaneous challenge with Josiah strain)</td>
<td>Cashman 2011</td>
</tr>
<tr>
<td><strong>Small Interfering RNAs</strong> (NP and L siRNA)</td>
<td>Inhibition of the replication of LASV from different lineages by up to 1 log</td>
<td>In vitro</td>
<td>Muller 2007</td>
</tr>
<tr>
<td><strong>Cocktail of Genistein and Tryphostin AG1478</strong> (kinase inhibitors)</td>
<td>95% with Pichinde virus at a dose of 100 mM Genistein/25 mM Tyrphostin; effect of the drug cocktail also demonstrated on LASV replication efficiency (by RT-PCR)</td>
<td>In vitro</td>
<td>Kolokoltsov 2012</td>
</tr>
<tr>
<td><strong>17C8, 17C9, 16G8</strong> (small molecule entry inhibitor)</td>
<td>Inhibition of the infection of human and primate cells with IC50 values of 500–800 nM</td>
<td>In vitro</td>
<td>Lee 2008</td>
</tr>
</tbody>
</table>
R&D needs - antivirals

Additional human studies and re-evaluation of the efficacy of ribavirin in all Lassa Fever patients

Equivalence trials of alternative dosing regimens of ribavirin

Clinical evaluation of favipiravir +/- ribavirin
   – pharmacokinetics, dosing, iv
Convalescent plasma

Evaluated with promising results in animal models, guinea pigs and Non-Human Primates

Mixed results obtained in human Lassa Fever cases
  – Additionally, unselective convalescent plasma may need to be concentrated to be therapeutically useful

=> Criteria for selection of human convalescent plasma are needed if such immunotherapy to be used therapeutically
Monoclonal antibodies

Limited data available to document their potential as a therapy against Lassa Fever

Promising results with human mAb/combinations tested in animal models

- mAb could be use either as pre-exposure prophylaxis or post-exposure treatment
- provided improvements of manufacturing processes result in lowering their costs

=> Criteria for clinical evaluation of monoclonal antibodies/combinations are needed
Four Strategic Goals

1. More fully evaluate ribavirin for treatment of Lassa fever and determine the appropriate role of ribavirin in clinical trials of new therapeutics

2. Develop, evaluate, and license new and improved affordable therapeutic agents for treatment of Lassa fever and prevention of Lassa fever-associated sequelae, as well as for PEP to prevent LASV infection, for multiple LASV lineages
Four Strategic Goals

3. Determine best strategies for treatment with therapeutic agents and supportive care for Lassa fever patients and develop applicable guidelines.

4. Continue to stimulate research into areas that will enhance prognostic capabilities for Lassa fever, such as use of biomarkers and quantitative assays for measuring viral load.