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Pharmacokinetics of the antiviral drug ribavirin in Lassa fever treatment

Submission date	Recruitment status	[_] Prospectively registered
02/02/2020	No longer recruiting	[X] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
06/02/2020	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
05/10/2022	Infections and Infestations	

Plain English summary of protocol

Background and study aims
Lassa fever (LF) is a severe and often fatal systemic disease in humans. It is caused by Lassa virus (LASV) which belongs to the segmented negative-strand RNA viruses of the family Arenaviridae. LF affects a large number of countries in West Africa. The currently used antiviral, which is also recommended by WHO, is ribavirin. However, evidence for ribavirin efficacy in LF patients is poor and pharmacokinetic (PK) data for currently used regimens are not available. This study will describe blood concentrations of ribavirin and will provide evidence for further dose optimization studies with the ultimate goal of improving patient care.

Who can participate?
Patients aged 18 years or older, suffering from Lassa fever.

What does the study involve?
Participants will receive ribavirin treatment using the Irrua hospital dosing regimen.
Blood samples will be collected at 0.5, 1, 3, 5, 8, 12 and 24 hours after doses on day 1, day 4 and day 10.

What are the possible benefits and risks of participating?
Benefits: Participants will be provided with protein bars and long-lasting insecticide-treated bednets as compensation for taking part in this observational study.
Risks: Participants may experience side effects from taking the drug.

Where is the study run from?
Irrua Specialist Teaching Hospital (Nigeria)

When is the study starting and how long is it expected to run for?
February 2020 to September 2021

Who is funding the study?
Federal German Ministry for Health (Germany)

Who is the main contact?
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Contact information

Type(s)
Public

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
v03 06DEC2019, amended version of v02 25OCT2019

Study information

Scientific Title
Prospective observational study on the pharmacokinetic properties of the Irrua ribavirin regimen used in routine clinical practice in Lassa fever patients in Nigeria

Acronym
PAIRR

Study objectives
Evaluating the pharmacokinetic (PK) characteristics of ribavirin when administered as per local standard in a national reference centre for treatment of Lassa fever (LF). Descriptive analysis of

drug exposure and viral kinetics will be performed to elucidate the PK/PD (pharmacodynamic) profile of ribavirin in the treatment of LF.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 07/11/2019, Human Research Ethics Committee of ISTH (Irrua Specialist Teaching Hospital, km87 Benin Auchi Road, Irrua, P.M.B. 8 Edo State, Nigeria; +234 815 299 8878; isth.rec.2015@gmail.com), ref: ISTH/HREC/20190104/009

Study design
Prospective observational clinical study

Primary study design
Observational

Secondary study design
Longitudinal study

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Part of the informed consent form

Health condition(s) or problem(s) studied
Lassa fever

Interventions
Pharmacokinetic analysis of ribavirin treatment
Blood samples will be collected at 0.5, 1, 3, 5, 8, 12 and 24 hours after doses on day 1, day 4 and day 10 of ribavirin treatment using the Irrua dosing regimen. Additionally, blood will be collected during screening before the first dose of ribavirin. Blood samples will be centrifuged and the plasma supernatant will be frozen at -80° C within 2 h after blood sampling. Plasma samples will be inactivated using a validated protocol. The samples will then be shipped frozen to the bioanalysis site (Dept. of Clinical Pharmacy, Institute of Pharmacy, University of Hamburg, Germany). Ribavirin plasma concentrations will be determined using liquid chromatography coupled to tandem mass spectrometry (LCMS/ MS).

PCR analyses
Blood for RT-PCR, LASV serology and metagenomic sequencing will be sampled at inclusion, 24 hours after first drug administration and then every second day until end of treatment. Two RT-PCR assays for the detection of LASV, Altona Diagnostics (Hamburg, Germany) and an inhouse assay will be used to determine the viral load. These analyses will be performed at site in Irrua.

Biochemistry and hematology
Blood for biochemical safety and tolerability will be collected every second day starting with

screening. Biochemistry and hematology analyses will be performed using automated systems at ISTH.

Intervention Type
Drug

Phase
Phase IV

Drug/device/biological/vaccine name(s)
Ribavirin

Primary outcome measure
Pharmacokinetic parameters (maximum concentration (Cmax), maximum time (Tmax), area under the curve (AUC), half-life time (T1/2), volume of distribution) using blood samples will be collected at 0.5, 1, 3, 5, 8, 12 and 24 hours after doses on day 1, day 4 and day 10 of ribavirin treatment using the Irrua dosing regimen

Secondary outcome measures
1. Safety and tolerability of the Irrua Ribavirin regimen measured using clinical, hematological, and biochemical parameters:
1.1. Clinical: every day from day 0 to day 10
1.2. Haematology: standarad full blood count (hb; wbc; pla; diff) every 48 hours
1.3. Biochemistry: creatinine; alt; ast; bun; ldh every 48 hours
2. Viral kinetics in patients measured using at day 0, 5, 10
3. LASV genome changes under the Irrua ribavirin regimen measured at day 0, 5, 10

Overall study start date
01/06/2019

Completion date
01/09/2021

Eligibility

Key inclusion criteria
1. Age ≥ 18 years
2. Lassa fever confirmed by RT-PCR
3. Written informed consent
4. Anticipated treatment with intravenous ribavirin

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
20

Total final enrolment
20

Key exclusion criteria
1. Inability to give consent (e.g. unconscious patients/ cognitively impaired patients)
2. Critical illness (based on investigator's clinical evaluation)
3. Severe malnutrition
4. Hemodialysis
5. History of hemophilia / bleeding disorder
6. Hematocrit <30 %
7. History of hemoglobinopathies (i.e., sickle-cell anaemia or thalassemia major)
8. Known intolerance to ribavirin
9. Known pregnancy
10. Women who plan to get pregnant within the upcoming 3 months
11. Patients who already received ribavirin within the last 7 days

Date of first enrolment
03/02/2020

Date of final enrolment
18/03/2021

Locations

Countries of recruitment
Nigeria

Study participating centre
Irrua Specialist Teaching Hospital
km87 Benin Auchi Road
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Sponsor information

Organisation
Bernhard Nocht Institute for Tropical Medicine

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Sponsor type
Research organisation

Website
https://www.tropmed-hamburg.de

ROR
https://ror.org/01evwfd48

Funder(s)

Funder type
Government

Funder Name
Bundesministerium für Gesundheit

Alternative Name(s)
Federal Ministry of Health, Germany, Federal Ministry of Health, BMG

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
Germany

Results and Publications

Publication and dissemination plan
All results will be published in agreement between the Sponsor and the PI in international peer-reviewed scientific journals with preference to open access journals.

Intention to publish date
01/06/2022

Individual participant data (IPD) sharing plan

Relevant data are within the manuscript and its supporting information files. The data underlying the results presented in the study are available from the corresponding author on reasonable request.

IPD sharing plan summary

Available on request, Published as a supplement to the results publication

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	16/04/2020	21/04/2020	Yes	No
Results article	outcome measures	26/07/2022	05/10/2022	Yes	No