EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 8
Issue: 2
50-54
Year: 2021

USE OF RIBAVIRIN IN THE TREATMENT OF LASSA FEVER: A SYSTEMATIC REVIEW

Peter Ekpunobi Chime[1*], Ethel Nkechi Chime[2,3], Titus Okpara[1]

[1]Department of Medicine, Enugu State University of Science and Technology Teaching Hospital, Parklane, Enugu, Nigeria.
[2]Department of Otorhinolaryngology, University of Nigeria Teaching Hospital, Ituku-Ozalla, Enugu, Nigeria.
[3]Department of Otorhinolaryngology, Enugu State University of Science and Technology Teaching Hospital, Parklane, Enugu, Nigeria.

***Corresponding Author: Peter Ekpunobi Chime**
Department of Medicine, Enugu State University of Science and Technology Teaching Hospital, Parklane, Enugu, Nigeria.
DOI: https://doi.org/10.17605/OSF.IO/EAHWB

Article Received on 05/12/2020 **Article Revised on 25/12/2020** **Article Accepted on 15/01/2021**

ABSTRACT
In Lassa fever endemic region of West Africa, ribavirin is the only recommended antiviral agent. Although, the effectiveness of ribavirin in Lassa fever treatment has been reported, questions have been raised regarding the efficacy and safety of ribavirin in Lassa fever patients with reduced aspartate aminotransferase levels. This article reviewed the various studies on the use of ribavirin in Lassa fever patients. Internet search was done for full articles on studies that evaluated Laser fever patients treated with ribavirin. The case fatality rates in Lassa fever were generally less in ribavirin treated patients than in non-ribavirin treated patients. Treatment with ribavirin was more effective when given early. Ribavirin had some adverse effects, but ototoxicity was not among the adverse effects reported on ribavirin. These retrospective studies did not address the issue of the effectiveness and safety of ribavirin in Lassa fever patients with reduced aspartate aminotransferase levels. Further studies are required to address the various shortcomings of these retrospective studies. However, randomized clinical trials recommended by some authors to address these shortcomings are likely to face some challenges.

KEYWORD: Treatment of Lassa fever, Ribavirin in Lassa fever, Lassa fever, Treatment of viral haemorrhagic fevers.

INTRODUCTION
Laser fever is one of the viral haemorrhagic fevers associated with significant morbidity and mortality in man. Lassa fever results from an infection by Lassa virus (LASV) from *Mastomys natalensis*.[1,2] Most cases of Lassa virus infection are asymptomatic or there may be mild symptoms.[2] However, mortality is high among hospitalized patients [1] and there is a high incidence of hearing loss among those who survived Lassa virus infection.[1] For this reason, an ideal antiviral agent for Lassa fever should not be ototoxic so as to not to increase the incidence of hearing loss in Lassa fever. Laboratory confirmation of Lassa fever should be done for any suspected case of Lassa fever.[3,4] For adult females suffering from Lassa fever, it is important to enquire about pregnancy and also to test for pregnancy if necessary, as pregnancy has prognostic implication for management outcome in Lassa fever, as well as therapeutic implication with ribavirin treatment.[5]

In Lassa fever, ribavirin is the specific therapeutic agent, an important addition to supportive care. It is widely in use in West Africa, including Nigeria.[6] Even in countries outside West Africa where it is not officially approved, ribavirin is the antiviral agent occasionally used in Lassa fever. However, it was noted that while ribavirin was beneficial to Lassa fever patients with elevated aspartate aminotransferase levels, it does not appear to be so in Lassa fever patients with reduced aspartate aminotransferase levels.[7] A proper randomized controlled clinical trial was recommended to re-examine the usefulness of ribavirin in Lassa fever. Although, Eberhardt et al did an extensive review on the use of ribavirin in Lassa fever, we considered it necessary to do another systematic review on this problem, a review that will not only examine the usefulness of ribavirin, but will also examine the adverse effects of ribavirin. This paper is aimed at systematically reviewing the usefulness and adverse effects of ribavirin in Lassa fever.

MATERIALS AND METHODS
Search was made for full articles on the treatment of Lassa fever with ribavirin, written in English. Electronic searches were made using PubMed and Google Scholar

databases, with the following keyword "*ribavirin use in Lassa fever."* The search returned 58 and 2230 articles respectively. Articles relevant to the scope of the review were identified. Their references were also checked for additional information. The protocol was published full text articles in English in which the sample size was not less than ten, and also in which there was laboratory confirmation of Lassa fever. All publications between 2011 and 2021 were considered. Out of all the full text articles that were retrieved, seven articles which met the inclusion criteria were included in the review. Data from those articles were retrieved and systematically reviewed. The data obtained were year of study, type of study, number of confirmed cases of Lassa fever, percentage of patients on ribavirin and the case fatality rate.

PHARMACOLOGY OF RIBAVIRIN

Ribavirin discovered in 1970, is a synthetic analogue of guanosine which is a purine nucleoside.[9] Ribavirin is available in tablet and capsule forms as well as in solutions. Inhalational form is available for children for the treatment of respiratory syncytial virus. The compound is stable at room temperature but when reconstituted for injection or inhalation, it should be discarded after 24 hours.[8]

Some of the Chemical Properties of Ribavirin:[8]
Chemical name: 1-beta-D-ribofuranosyl-1, 2, 4-triazole-3-carboxamide
Molecular formula: $C_{10}H_{13}N_5O_5$
Molecular Weight: 244.2 g/mol
Formal Charge: 0
Physical properties: Colorless, odorless, tasteless, water-soluble white crystalline powder.

Decomposition: If heated, it decomposes and emits nitrogen oxide which is toxic.

The chemical structure of ribavirin is shown in Figure 1.

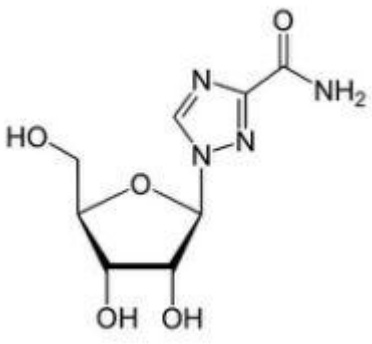

Figure: 1. The chemical structure of ribavirin.

Ribavirin when taken orally is metabolized by the liver and eliminated primarily through the kidney. Dose adjustment of ribavirin is recommended in renal insufficiency.[5,9] while it should be avoided in severe renal impairment. Ribavirin triphosphate is an active metabolite of ribavirin.[9,10] Ribavirin has a long terminal half-life. Its exact mechanism of action is not well known, but it is known to inhibit normal viral replication. Inhibition of RNA dependent RNA polymerase is one of its postulated mechanisms of action.[9, 10] Experimental studies have shown ribavirin to be effective against a number of RNA viruses as well as a number of DNA viruses (e.g., Lassa virus, hepatitis C virus, hepatitis A virus, respiratory syncytial virus, foot-and-mouth disease virus, West Nile virus and SARS-Cov 1, the aetiological agent for severe acute respiratory syndrome).[5,9,10,11, 12] Its multiple mechanisms of action was thought to underlie its broad spectrum anti-viral activity.

The contraindications to the use of ribavirin, precautions, drug interactions and laboratory monitoring for patients on ribavirin, can be found in the paper by Koren et al.[9] Although their discussion was in respect of ribavirin use in SARS, it also applies to ribavirin use in Lassa fever.

Ribavirin was approved by the United States in 1986, and also by Canada, for the treatment of respiratory syncytial virus. Canada[9] and the United States also approved ribavirin for the treatment of hepatitis C virus infection in combination with interferon alfa. In the Lassa fever endemic region, including Nigeria, ribavirin is approved for the treatment of Lassa fever.[6] It is recommended for post-exposure prophylaxis for high risk contacts.[13] For the treatment of Lassa fever, the details are well outlined in the WHO protocol.[5] Ribavirin is also used for the treatment of severe acute respiratory syndrome (SARS).[9] In 2018 WHO called for re-evaluation of ribavirin use in Lassa fever.[14]

FINDINGS ON RIBAVIRIN USE IN THE TREATMENT OF LASSA FEVER

The characteristic features of the seven studies that were reviewed are provided in Table 1.

Ehichioya et al[15] reported on 25 confirmed cases of Lassa fever in which 84% of them received ribavirin. The overall case fatality rate was 29%.

In the study by Asogun et al[16] there were 170 Lassa fever patients with known outcomes and many of them received ribavirin. The overall case fatality rate was 36%. Late presentation of Lassa fever patients to the hospital was one of the challenges they noted. Another challenge was that about one-half of the patients who died did not have enough time for intervention with ribavirin.

Ajayi et al[17] reported the use of ribavirin in ten confirmed cases of Lassa fever and ten suspected cases of Lassa fever. Among the confirmed cases in which 70% of them received ribavirin, there was a statistically significant difference in the case fatality rate between those who received ribavirin and those who did not receive ribavirin. The overall case fatality rate was 40%.

In the study by Dahmane et al,[18] the case fatality rate among the 20 patients who received ribavirin was 40%, while the case fatality rate among the 16 patients who did not receive ribavirin was 87%. They also reported that the case fatality rate was much less when ribavirin was started within six days of admission. Some of the reasons for not receiving ribavirin were death on arrival or shortly after arriving at the hospital.

Buba et al[19] reported on 47 confirmed cases of Lassa fever in which the case fatality rate was less in ribavirin-treated group than in the untreated group. The overall case fatality rate was 59.6%.

Okokhere et al[20] studied 291 confirmed Lassa fever patients in which all of them received ribavirin. Ribavirin was found to be effective. Ribavirin was found to be more effective when given within six days from the onset of disease. Mortality was higher when ribavirin was started after two weeks from onset of illness (20%) than when it was started one week from onset of illness (2%).

Abdulkarim et al[21] studied on 57 confirmed cases of Lassa fever and reported a very high case fatality rate. Late presentation of patients to the hospital was a major challenge.

In the studies reviewed, none of the authors reported on the adverse effects of ribavirin on their patients.

Table 1: The characteristics of the studies under review.

	Type of study	Sex Male:female	Confirmed cases (n)	Ribavirin given (%)	Case fatality rate (CFR)
Ehichioya et al, 2012[15]	Retrospective study	15:10	25	84%	29% overall
Asogun et al, 2012[16]	Retrospective study	-	170	Many of them	36% overall
Ajayi et al, 2013[17]	Retrospective study	-	10	70%	40% overall
Dahmane et al, 2014[18]	Retrospective study	20:16	36	56%	61% overall 40% in treated group 87% in untreated group
Buba et al, 2018[19]	Retrospective study	30:17	47	40.4%	59.6% overall 31.6% in treated group 78.6% in untreated group
Okokhere et al, 2018[20]	Retrospective study	170:121	291	100%	24% overall
Abdulkarim et al, 2020[21]	Retrospective study	54%:46%	76		54%

Key: Ribavirin given, percentage of patients who received ribavirin.

POST-EXPOSURE PROPHYLAXIS

Iroezindu et al[22] reported on 121 primary contacts of Lassa fever made up mainly of hospital staff and medical students. Out of these, 20 (16.5%) had high risk exposure out of which 18 of them received prophylactic ribavirin therapy. No secondary infection occurred among the treated and untreated 121 primary contacts. It has been previously reported that secondary attack rates in Lassa fever are relatively low.[11] For that reason, post-exposure prophylaxis has been recommended only for high-risk contacts.

The adverse effects of ribavirin noted in the high risk contacts on ribavirin in the study by Iroezindu et al were fatigue, dizziness, abdominal pain, palpitations, anorexia, sleep disturbance, skin rash and headache.[22] In the report by Hadi et al, also on post-exposure prophylaxis in Lassa fever contacts, similar adverse effects were reported in addition to anxiety, depression, diarrhea, tremor, nausea and fever.[13] As pointed out by Hadi et al, some of the observed symptoms in the Lassa fever contacts on post-exposure prophylaxis might be psychosomatic symptoms arising from the fear that they had contacted Lassa fever. Such fear could result in anxiety, palpitations and sleeplessness.

Lassa fever contacts on post-exposure prophylaxis offer a very good opportunity for the observation of adverse effects that may be solely ascribed to ribavirin. This is because of the possibility that the symptoms of Lassa fever may overlap with the assumed adverse effects of ribavirin in symptomatic Lassa fever patients who are on ribavirin.

DISCUSSION

Findings from the Analysis of the Various Studies Reviewed

From the studies reviewed, case fatality rates were generally less in ribavirin treated group than in non-ribavirin treated group. Ribavirin was more effective when given early in the course of the disease, within six days of onset of illness. Case fatality rate even in the ribavirin-treated group was age dependent, being higher in the older age group. There was no evidence that ribavirin was ototoxic, although the studies reviewed did

not address the issue of adverse effects generally. These retrospective studies did not address the issue of the effectiveness and safety of ribavirin in Lassa fever patients with reduced aspartate aminotransferase levels.

Another important thing noticed in these studies was that patients who were unable to receive ribavirin before death were likely to find themselves in the non-treatment arm of the study, which might introduce bias with the possibility of overestimating the effect of treatment with ribavirin. This was one of the issues raised by Eberhardt et al[7] against these retrospective studies.

WHAT IS KNOWN FROM PREVIOUS REPORTS

(a) From previous reports, ribavirin was shown to be effective in some group of Lassa fever patients[7] The present concern is about patients with reduced aspartate aminotransferase level, whether the use of ribavirin in this class of patient would be deleterious or beneficial.[7]

(b) Ribavirin use in man is not new. It is used for the treatment of respiratory syncytial virus infection in children in which there is both clinical effectiveness and tolerability.[11] It is also used in the treatment of hepatitis C infection in combination with interferon alfa.[9] There has been no report of ototoxicity relating to ribavirin when used in those medical conditions.

(c) A proper randomized controlled clinical trial on ribavirin in Lassa fever has been advocated to address the shortcomings observed in the retrospective studies.[7]

CHALLENGES FACING RANDOMIZED CONTROLLED CLINICAL TRIAL ON RIBAVIRIN

(a) Randomized clinical trial on Lassa fever is only possible in West Africa where Lassa fever is endemic with yearly outbreaks.[5]

(b) Randomized clinical trial means that Lassa fever patients will be randomly assigned to ribavirin treatment group and non-ribavirin treatment group.

(c) How easy is it for ethical approval to be obtained for such a study in which some patients with such serious disease will be denied of ribavirin treatment just for the purpose of research?

(d) Even if it is possible to obtain ethical approval for such a study, how many patients will be willing to give their consent to such a study in which they may be denied full treatment for a disease that is associated with significant morbidity and mortality as well as stigmatization?

CONCLUSION

Lassa fever has been with us since 1969, and its yearly outbreaks in West Africa come with significant morbidity and mortality. Despite our very long association with Lassa fever and ribavirin, there is yet no consensus on ribavirin being a universally accepted antiviral agent for Lassa fever. Randomized controlled clinical trials had been recommended to address the shortcomings of the previous retrospective studies on ribavirin, but the randomized clinical trials are likely to face some challenges.

REFERENCES

1. World Health Organization. Lassa fever Fact sheet, 2017.http://www.who.int/mediacentre/factsheets/fs179/en/ [Accessed 2 January, 2021]
2. Centers for Disease Control and Prevention. Lassa Fever.https://www.cdc.gov/vhf/lassa/transmission/index.html[Accessed 2 January, 2021]
3. Niklasson BS, Jahrling PB, Peters CJ. Detection of Lassa virus antigens and Lassa virus-specific immunoglobulins G and M by enzyme-linked immunosorbent assay. *J Clin Microbiol*, 1984; 20(2): 239-244.
4. Bausch DG, Rollin PE, Demby AH et al. Diagnosis and clinical virology of Lassa fever as evaluated by enzyme-linked immunosorbent assay, indirect fluorescent-antibody test, and virus isolation. *J Clin Microbiol*, 2000; 38(7): 2670-2677.
5. WHO. APPLICATION FOR INCLUSION OF RIBAVIRIN IN THE WHO MODEL LIST OF ESSENTIAL MEDICINES https://archives.who.int/eml/expcom/expcom15/applications/newmed/ribaravin/ribavirin.pdf [Accessed 2 January, 2021]
6. Nigeria Centre For Disease Control. Viral haemorrhagic fevers preparedness and response plan, 2017. Available from: https://ncdc.gov.ng/themes/common/docs/protocols/24_1502192155.pdf. [Accessed 2 January, 2021].
7. Eberhardt KA, Mischlinger J, Jordan S, Groger M, Gunther S, Ramharter M. Ribavirin for the treatment of Lassa fever: A systematic review and meta-analysis. *International journal of infectious diseases*, 2019; 87: 15 - 20.
8. National Center for Biotechnology Information. PubChem Ribavirin (Compound). https://pubchem.ncbi.nlm.nih.gov/compound/ribavirin [Accessed 2 January, 2021].
9. Koren G, King S, Knowles S, Phillips E. Ribavirin in the treatment of SARS: A new trick for an old drug? CMAJ, 2003; 168: 1289-1292.https://www.cmaj.ca/content/168/10/1289 [Accessed 2 January, 2021].
10. Graci JD, Cameron CE. Mechanisms of action of ribavirin against distinct viruses. Rev. Med. Virol, 2006; 16: 37–48. https://www.onlinelibrary.wiley.com/doi/pdf/10.1002/rmv.483
11. Hall CB, Granoff DM, Gromisch DS, Halsey NA, Kohl S, Marcuse EK, Marks MI et al (Committee on Infectious Disease). Use of Ribavirin in the Treatment of Respiratory Syncytial Virus Infection. *Pediatrics*, 1993; 92; 501 - 504.

https://pediatrics.aappublications.org/content/pediatrics/92/3/501.full.pdf
12. Chaudhary RK, Andonov AP. Effect of ribavirin on hepatitis A virus replication in vitro. *Can J Infect Dis*, 1992; 3(2): 67-70. doi:10.1155/1992/531837
13. Hadi CM, Augustine A, Khan SH, Bangura J, Sankoh M, Koroma S, Juana B, Bah A, Coulibaly M, Bausch DG. Ribavirin for Lassa Fever Postexposure Prophylaxis. Emerging Infectious Diseases, 2010; 16(12). www.cdc.gov/eid.
14. World Health Organization. Efficacy trials of Lassa Therapeutics: endpoints, trial design, site selection. WHO Workshop; 2018 Final Report. https://www.who.int/blueprint/what/norms-standards/LassaTxeval_FinalmeetingReport.pdf?ua=1 [Accessed 7 January 2021].
15. Ehichioya DU, Asogun DA, Ehimuan J, Okokhere PO, Pahlmann M, Olschläger S, Becker-Ziaja B, Günther S, Omilabu SA. Hospital-based surveillance for Lassa fever in Edo State, Nigeria. *Trop Med Int Health*, 2012; 17(8): 1001-4.
16. Asogun DA, Adomeh DI, Ehimuan J, et al. Molecular diagnostics for Lassa fever at Irrua specialist teaching hospital, Nigeria: lessons learnt from two years of laboratory operation. *PLoS Negl Trop Dis*, 2012; 6(9): 1839. doi:10.1371/journal.pntd.0001839.
17. Ajayi N.A. Nwigwe C.G. Azuogu B.N. Onyire B.N. Nwonwu E.U. Ogbonnaya L.U. et al. Containing a Lassa fever epidemic in a resource-limited setting: outbreak description and lessons learned from Abakaliki, Nigeria (January–March 2012). *Int J Infect Dis*, 2013; 17: 1011-6.
18. Dahmane A, van Griensven J, Van Herp M, Van den Bergh R, Nzomukunda Y, Prior J, et al. Constraints in the diagnosis and treatment of Lassa Fever and the effect on mortality in hospitalized children and women with obstetric conditions in a rural district hospital in Sierra Leone. Trans R Soc Trop Med Hyg, 2014; 108: 126–32.
19. Buba M.I., Dalhat M.M., Nguku P.M., Waziri N., Mohammad J.O., Bomoi I.M. et al. Mortality among confirmed Lassa fever cases during the 2015–2016 outbreak in Nigeria. *Am J Public Health*, 2018; 108: 262-264.
20. Okokhere P, Colubri A, Azubike C, et al. Clinical and laboratory predictors of Lassa fever outcome in a dedicated treatment facility in Nigeria: a retrospective, observational cohort study. Lancet Infect Dis, 2018; 18(6): 684-695.
21. Abdulkarim MA, Babale SM, Umeokonkwo CD, Bamgboye EA, Bashorun AT, Usman AA, et al. Epidemiology of Lassa Fever and Factors Associated with Deaths, Bauchi State, Nigeria, 2015–2018. Emerg Infect Dis, 2020; 26(4): 799-801.
22. Iroezindu MO, Unigwe US, Okwara CC, Ozoh GA, Ndu AC et al. Lessons learnt from the management of a case of Lassa fever and follow-up of nosocomial primary contacts in Nigeria during Ebola virus disease outbreak in West Africa. Tropical Medicine and International Health, 2015; 20(11): 1424 – 1430.