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Review

Ribavirin for the treatment of Lassa fever: A systematic review and meta-analysis

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ABSTRACT

Objectives: Lassa fever (LF) causes annual outbreaks in endemic regions with high mortality of symptomatic patients. Ribavirin is recommended as standard treatment for LF in national and international guidelines but the evidence base for this recommendation has been questioned recently.
Methods: We conducted a systematic review and included 6 studies providing efficacy data of ribavirin treatment for LF (PROSPERO protocol CRD42018103994).
Results: Besides retrospective case series, the evidence mostly relies on a single prospective clinical trial with critical risk of bias. In this trial, LF associated mortality is reduced for patients with elevated aspartate aminotransferase (AST) when treated with ribavirin (OR 0.41, 95% CI 0.23–0.73), while mortality is higher for patients without elevated AST (OR 2.37, 95% CI 1.07–5.25).
Conclusions: Based on the available data, current treatment guidelines may therefore put patients with mild LF at increased risk of death. The role of ribavirin in the treatment of LF requires urgent reassessment.

Contents

Background

Lassa fever (LF) is a zoonotic disease associated with acute and potentially fatal haemorrhagic disease caused by Lassa virus (LASV), a member of the *Arenaviridae* virus family. It is endemic in several West African countries and occurs sporadically as well as in annual outbreaks (Fichet-Calvet and Rogers, 2009). Although LASV can be transmitted between humans, the majority of cases is thought to be transmitted by contact with urine or faeces of the widespread commensal rodent *Mastomys natalensis. Mastomys erythroleucu* and *Hylomyscus pamfi* might also play a role in disease transmission (Mari Saez et al., 2018).

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LF is estimated to cause up to 300,000 cases and 5,000 deaths per year in endemic regions of West Africa (Günther and Lenz, 2004). In 2018 and 2019, Nigeria experienced a large increase in the number of cases during the endemic peak season, which are thought to be at least in part a result of increased awareness and intensified case detection measures (Kafetzopoulou et al., 2019). However, despite improved diagnostic capacities for early detection and treatment, the absolute numbers of deaths and the overall case fatality rate (CFR) remain unsatisfactorily high.

Clinically, LF is difficult to distinguish from other febrile illnesses endemic in West Africa (Mertens et al., 1973). Symptoms include fever, pharyngitis, gastrointestinal complaints, and cough. In later stages bleeding, facial oedema, convulsions, pericardial effusions and coma are commonly observed (Ehichioya et al., 2012; Knobloch et al., 1980; Monson et al., 1987; Troup et al., 1970). Although the CFR among hospitalised patients may exceed 50% during outbreaks, most cases remain mild or even asymptomatic (Fraser et al., 1974; McCormick et al., 1987; Shaffer et al., 2014). Underlying mechanisms for varying clinical courses of LF are unknown (Khan et al., 2008).

In contrast to Ebola virus disease, there is currently no advanced vaccine candidate available (Lukashevich et al., 2019). Treatment of LF is largely supportive and no antiviral drug has been approved by the United States Food and Drug Administration or the European Medicines Agency. Despite concerns regarding toxicity and lack of specificity, ribavirin (1-b-d-ribofuranosyl-1,2,4-triazole-3-carboxamide), a guanosine analogue that is active against a broad spectrum of DNA and RNA viruses has become an accepted off-label treatment for LF and is the recommended standard treatment for LF patients in national and international guidelines (Bausch et al., 2010; Nigeria Centre for Disease Control, 2017; World Health Organization, 2016). These recommendations are however based largely on a single clinical trial, performed in Sierra Leone in 1986 by McCormick et al., which suggests a beneficial effect of ribavirin, especially when given within the first six days after onset of symptoms (McCormick et al., 1986). However, due to the non-specific nature of symptoms treatment initiation is often late and associated with adverse treatment outcome (Shehu et al., 2018). Furthermore, the mode of action of ribavirin in LF is still unclear. It efficiently suppresses the replication of LASV in *vitro* but showed only moderate efficacy in reducing viremia *in vivo* (Bausch et al., 2010; Oestereich et al., 2016). Instead, ribavirin was found to protect infected cells from cell-death, thereby significantly reducing the circulation of cell damage markers such as aspartate aminotransferase (AST) rather than suppressing viral transmission, viral production, or enhancing the host's immune response in animal models (Carrillo-Bustamante et al., 2017). Particularly, a viral load "plateau" in mice was observed by Carrillo-Bustamante

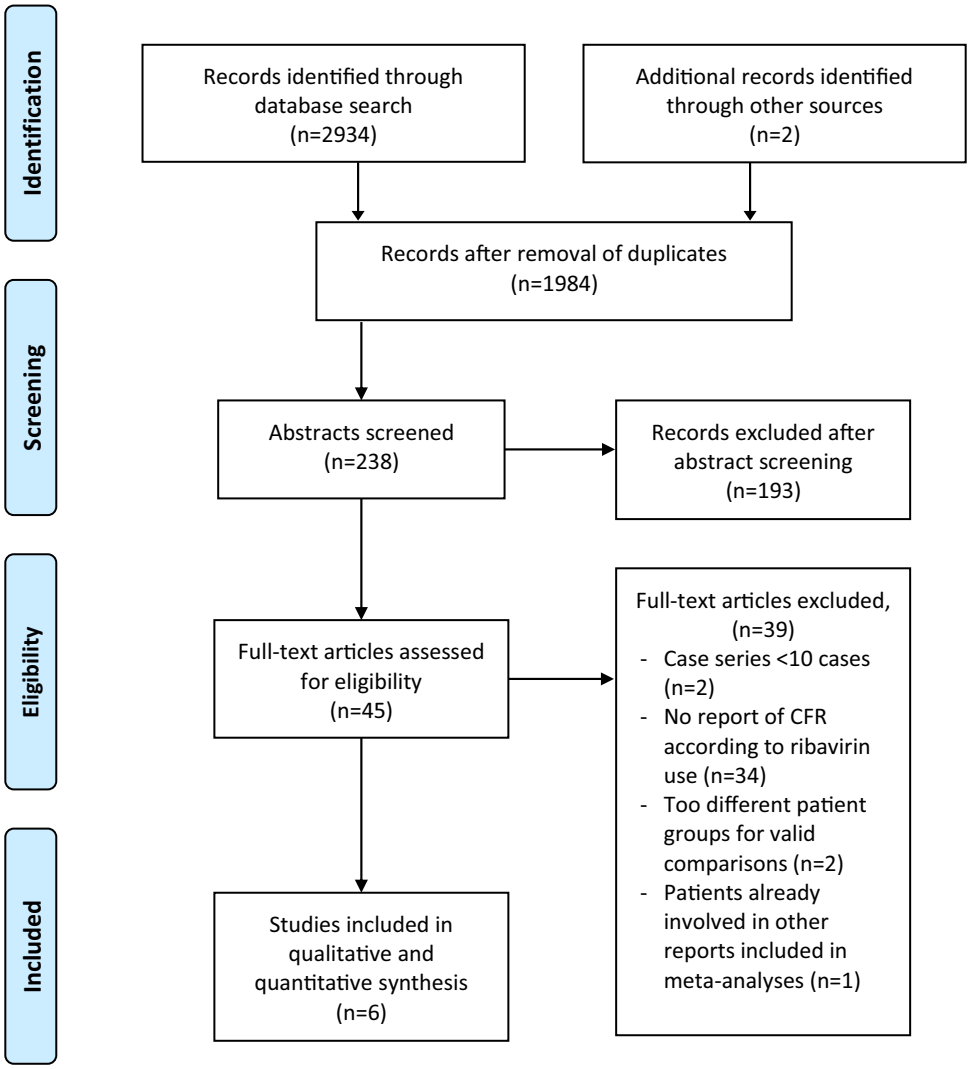

Figure 1. PRISMA Flow chart of study selection.

et al., which could be explained by the resulting longer survival of infected cells when treated with ribavirin, allowing for more viral production.

Based on these data, the recommendation of ribavirin has been increasingly questioned by international experts and the World Health Organization (WHO) (World Health Organization, 2018). To address these concerns, additional data of the original prospective trial by McCormick et al. were released in March 2019 and a re-analysis was performed by independent experts. (Final Report Analysis, 1992; Ludwig, 2019)

Given the significant threat to public health in West Africa, the constant risk of spread from endemic regions and the absence of approved drugs or vaccines, the WHO has listed LF as a priority disease for urgent research and development (Mehand et al., 2018). The recently released revised results of the only clinical trial provide the opportunity to re-evaluate objectively the efficacy of ribavirin for the treatment of patients with LF in the context of other published evidence of ribavirin for LF. This systematic review contributes to LF research by summarizing all currently available evidence on the efficacy of ribavirin for the treatment of patients with LF by pooling all available studies.

Methods

Search strategy and selection criteria

This study was performed as a systematic review and meta-analysis of all published and available evidence providing information on the efficacy of intravenous ribavirin for the treatment of LF. All randomised clinical trials, non-randomised studies, cohort studies, case-control studies, and case series with a minimum of 10 LF cases were considered for this systematic review. No restriction on the age of patients, publication date, language, or publication status was applied for the inclusion of respective studies. This systematic review was conducted following the PRISMA guidelines and the protocol was registered with PROSPERO (PRISMA checklist: Supplementary Fig. S1, PROSPERO protocol number: CRD42018103994). Articles were identified between February 2019 and March 2019 by electronic searches of PubMed, CINAHL, Science Citation Index Expanded, and Emerging Sources Citation Index, using "(lassa) NOT lassa[Author]" as search term and by checking bibliographies of included studies. Two investigators performed the literature search independently and discrepancies were resolved by discussion and consensus. Additionally, Conference Proceedings Citation Index-Science, ClinicalTrials.gov, and EU Clinical Trials Register were searched to identify currently ongoing and not yet published trials. Experts in the field were contacted to request information about grey literature. PROSPERO and the Cochrane Library were checked for similar systematic reviews.

Data extraction and analysis

Data from included studies were extracted independently by the first two authors. Discussion of discrepancies and consultation of the last author led to a complete dataset for analysis. The variable extracted was CFR according to treatment with or without intravenous ribavirin. Risk of bias of individual studies was assessed using the ROBINS-I tool (Sterne et al., 2016). The certainty of evidence was determined using the GRADE approach and the GRADEpro GDT software (GRADEpro Guideline Development Tool, McMaster University, 2015) (Schünemann et al., 2013).

Odds ratios (OR) with their 95% confidence intervals (CI) for dichotomous outcome measures were obtained using Mantel–Haenszel random effects models. Heterogeneity was assessed by visual inspection of forest plots and quantified by the I^2 statistic. Meta-analyses and forest plots were computed using the RevMan software (Review Manager Version 5.3, Copenhagen, 2014).

Results

We identified 2934 records from electronic literature search and two further references by contacting experts in the field (Figure 1). From these, we counted 1984 unique references after removing duplicates. We further removed 1746 references with results of *in vitro* or animal models only, reviews without patient data, or studies focussing on other diseases than LF by screening of titles. We screened abstracts of 238 records and considered 193 references to be irrelevant for our review (narrative reviews, editorials, studies covering fewer than ten clinical cases, no mortality rates reported according to intravenous ribavirin use). 45 full-text articles were considered for inclusion, of which we excluded 39 at the full-text screening stage because subjects were overlapping with other reports already included in the meta-analysis or of similar reasons as above (Supplementary Table S1). We included 6 studies in our systematic review and meta-analysis (Table 1, Supplementary Table S2).

Efficacy of ribavirin for the treatment of LF

We identified five retrospective cohort studies with 372 participants (Ajayi et al., 2013; Asogun et al., 2012; Buba et al., 2018; Dahmane et al., 2014; Shaffer et al., 2019) and one prospective clinical trial with 894 participants meeting our inclusion criteria (Final Report Analysis, 1992). Doses of intravenous ribavirin treatment varied slightly between studies (Supplementary Table S3). The length of follow-up was not specified but most studies relied upon discharge from hospital as the primary endpoint.

In the pooled analysis of the included retrospective studies, 104 fatalities occurred in 272 individuals receiving parenteral ribavirin versus 83 deaths in 100 patients not receiving ribavirin (Figure 2). Despite the presence of a moderate heterogeneity, the synthesis demonstrates that patients who died were more often not treated with ribavirin (OR 0.13, 95% CI 0.04–0.40, $I^2 = 55\%$). However, patients in all studies were retrospectively allocated into analysis groups based on whether ribavirin treatment was initiated or not. This procedure included late presenting patients dying before treatment with ribavirin could be initiated, leading to a critical risk for bias of these reports by overestimating the treatment effect of

Table 1
Characteristics of studies included in the systematic review.

Study	Study type	Country	Number of LF positive patients	CFR in %
Ajayi et al. (2013)	Retrospective cohort study	Nigeria	10	40
Asogun et al. (2012)	Retrospective cohort study	Nigeria	198	31
Buba et al. (2018)	Retrospective cohort study	Nigeria	47	60
Dahmane et al. (2014)	Retrospective cohort study	Sierra Leone	36	61
Shaffer et al. (2014)	Retrospective cohort study	Sierra Leone	190	69
U.S. Centers for Disease Control and Sierra Leone Ministry of Health Studies, 1992	Prospective clinical trial	Sierra Leone	1853	18

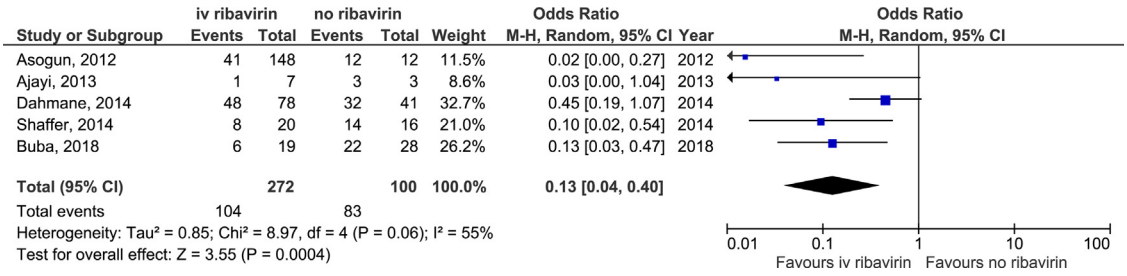

Figure 2. Forest plot of retrospective cohort studies evaluating the efficacy of intravenous ribavirin versus no ribavirin on the outcome mortality in patients with Lassa fever.

ribavirin and therefore to a very low certainty of evidence (Supplementary Tables S4 and S5).

Only one prospective clinical trial was identified evaluating the efficacy of ribavirin for the treatment of LF. The original publication of this trial by McCormick et al. provided results of patients with elevated transaminases only (McCormick et al., 1986). Instead of randomizing patients to treatment or control arm, the authors made use of data from a historic cohort as control group and pooled data from treatment groups that were judged not having an effect in retrospect. It remains unclear how participants were selected and allocated in the respective groups for analysis. Furthermore, randomization of participants in the treatment arm to distinct treatment options was unreliable. During the course of the clinical trial, important deviations from the study protocol occurred: distinct treatment groups were joined and patients with normal AST level were recruited to a lower extent apparently following an interim analysis. Because of these shortcomings of the original report, an extended version of the study data was recently made publicly available covering outcomes of all study participants from the original prospective clinical trial (Final Report Analysis, 1992). Subgroup analysis according to AST level of this newly released data demonstrates that mortality was reduced for patients of this trial presenting with elevated AST level when treated with ribavirin versus not being treated with ribavirin (OR 0.41, 95% CI 0.23–0.73). However, ORs for mortality were higher in LF patients without elevated transaminases at presentation when receiving ribavirin versus not being treated with ribavirin (OR 2.37, 95% CI 1.07–5.25, Figure 3). However, despite the provided additional results, this extended data version of the original trial has critical risk of bias due to missing data, misclassifications of participants to non-LF patients, and unreliable randomization and treatment allocation procedures (Supplementary Tables S4 and S5).

Discussion

This systematic review reveals two main findings. First, although LF was discovered 50 years ago and despite the high local burden and the constant risk of spread to non-endemic regions, treatment options are still very limited. International guidelines recommending therapy with ribavirin are based largely on evidence stemming from the original report of a single prospective clinical trial and a few available retrospective cohort studies. As shown in the assessment of this study, this report suffers from serious limitations. The clinical trial was apparently not conducted following the original study protocol as criteria for recruitment into the trial were modified following interim analysis. Importantly, this study was not a properly randomized controlled clinical trial as the comparator group was constituted retrospectively combining treatment groups with heterogeneous baseline characteristics and groups with different interventions. Notably, the comparator group was not recruited at the same time as the active treatment group but was rather a historic control. This opens the risk for bias due to improvement of supportive care during the study, which is known to be associated with an improved survival of patients with LF. In summary the assessment of the only prospective clinical trial reveals evidence of very low certainty due to critical limitations in the conduct, analysis and reporting of the clinical trial. Likewise, retrospective studies included in this review were assessed as having critical risk of bias. This limitation stems on the one hand from their retrospective study design and from methodological limitations in the analysis of the patient data by not taking into account the preferential allocation of severely ill and late presenting patients into the comparator group when death occurs prior to ribavirin treatment initiation. In analogy to other viral diseases such as Crimean–Congo hemorrhagic fever or influenza, late treatment initiation

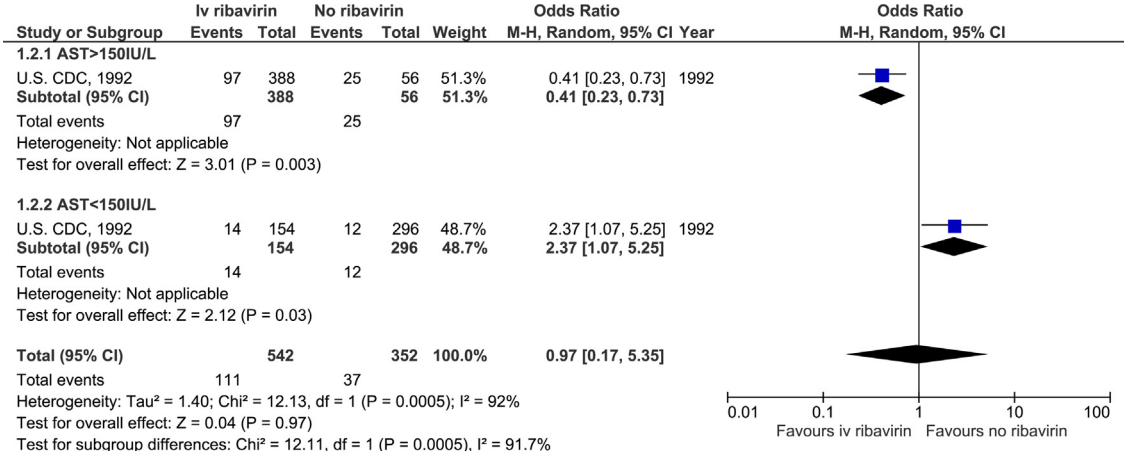

Figure 3. Forest plot of a prospective clinical trial evaluating the efficacy of intravenous ribavirin versus no ribavirin according to AST level on the outcome mortality in patients with Lassa fever.

may not have a measurable impact on disease outcome, underlining the importance of early treatment initiation in viral infections in general. In agreement with a recent WHO expert meeting, this analysis therefore concludes that current international and national treatment guidelines recommending ribavirin treatment for all patients with LF lacks solid evidence (World Health Organization, 2018).

Second, the recently released additional data and re-analysis of the prospective trial data unravel some new and highly important aspects on ribavirin treatment of patients with LF. Whereas ribavirin therapy was associated with a reduced mortality in LF patients with high levels of AST in this trial, patients with normal levels of transaminases had higher ORs for a fatal disease outcome when treated with intravenous ribavirin compared to patients receiving supportive therapy only (Final Report Analysis, 1992; Ludwig, 2019). This finding contradicts current treatment recommendations and medical practice in endemic regions encouraging the use of ribavirin even for mild cases (Okokhere et al., 2018). A potentially harmful effect of ribavirin in LF patients without elevated AST levels is pathophysiologically conceivable as ribavirin apparently has little antiviral properties and may be associated with higher viraemia, which may be disadvantageous in mild cases of LF (Carrillo-Bustamante et al., 2017; Oestereich et al., 2016). This practice ultimately might in part contribute to the unsatisfactorily high CFR of LF despite improved diagnostic and treatment infrastructure.

At the same time this finding raises important concerns for the role of ribavirin as post-exposure prophylaxis for LF. In this indication the risk benefit analysis may rather suggest withholding ribavirin based on the current evidence from mild LF cases. Future research should focus on the question of whether potentially harmful effects of ribavirin in patients without severe cell damage are caused by direct toxic effects, or by an increase in viral load due to enhanced survival of virus producing cells (Carrillo-Bustamante et al., 2017; Gowen et al., 2008). Randomised controlled trials are required to investigate the efficacy of ribavirin in different subgroups and indications and answer the question whether lower doses of ribavirin or shorter treatment durations could have similar properties of cell protection with at the same time a lower risk of unfavourable effects (Khan et al., 2008).

In conclusion, the efficacy of ribavirin for treating Lassa fever is uncertain because of critical risk of bias in underlying studies. Recently released data from a prospective trial, originally published in 1986, suggest a beneficial effect in patients with severe forms of LF and a potentially harmful effect in patients with mild forms of the disease. Re-assessment of the benefit of ribavirin in the treatment of LF seems urgently required.

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Conflict of interest statement

All authors declare no conflict of interests.

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