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Lassa Fever: Current Treatment and Prospects of an Effective Vaccine

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Review Article

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Abstract

Lassa fever (LF) has been a topical viral haemorrhagic fever with recurrent outbreaks in parts of West Africa where it has been endemic for some decades. It is a zoonotic disease with fatality of about 1% in the on-going outbreak in Nigeria. LF is responsible for the death of about 5,000 people annually, but till date has no preventive vaccine. In this paper we presented a brief virology of the causative agent of LF and reviewed the clinical presentation, requisite precautionary measures, diagnosis and current treatment of the virus infection. In addition the frontline vaccine candidates and prospects of having a prophylactic vaccine for Lassa fever are highlighted.

Keywords: Lassa Fever; Treatment; Vaccine; Ribavirin; Viral Hemorrhagic Fever

Abbreviations: LF: Lassa fever; LASV: Lassa Fever Virus; GPC: Glycoprotein Precursor Complex; WHO: World Health Organization.

Introduction

Lassa fever (LF) is one of the viral haemorrhagic fevers [1]. Human beings acquire the infection from contact with the urine or excreta of the carrier rat called Mastomys natalensis [2,3]. The causative micro-organism, Lassa fever virus (LASV), was isolated in 1969 in the town of Lassa in Borno State of Nigeria although the illness was first described in the 1950s [4-6]. LF has an incubation period of 5-21 days and the duration of the illness is typically 2-21 days. The disease is endemic in West African nations particularly Sierra Leone, Liberia, Guinea, Benin Republic, Nigeria, Ghana, and Mali [7]. Nigeria's latest outbreak has resulted in more than 130 deaths within 9 months. However cases of LF have been seen in the USA and some other non-African countries presumably due to international travels to and fro endemic countries and in the search of efficacious treatment [8-10]. Approximately 100,000 to 500,000 LF cases occur annually with about 5000 deaths annually [4,11]. Only about 20% of persons infected with LASV actually develop clinical LF whereas about 80% of infected people remain asymptomatic [12].

LASV itself is an emerging virus with epidemic potential [13] and has been listed among the pathogens that require Biosafety level 4-equivalent containment. It is an arenavirus and belongs to the Arenaviridae virus family. It is an enveloped virus with pleomorphic virions having filamentous helical nucleocapsids. It has

ambisense genomic configuration with bisegmented negative sense single stranded RNA genome [14,15]. LASV is one of the most clinically significant viruses among the members of the arenaviridae virus family [16]. It has a surface molecule named Glycoprotein Precursor Complex (GPC) which mediates both the binding of the virus to host cells and viral entry into host cells. GPC is a key element in the vaccinology of LF [17].

The primary target cells of LASV on entry into the human body are the antigen presenting cells (macrophages and dendritic cells). The state of activation of the antigen presenting cells (APCs) on challenge with LASV is an early determinant of how the infection will evolve. Typically in LASV infection, APCs tend to express ineffective antigen processing and presentation activity as a result of failure to undergo activation and maturation [14,18].

Type 1-IFN response is a key mediator of protection in LF infection. Up-regulation of IFNα signaling soon after LASV infection is a determinant of good outcome after exposure to LASV. Apparently where LASV is able to alter or suppress effective type 1 IFN response would lead to increased LASV replication and impaired innate and adaptive immune responses leading to poor viral challenge and progression of the disease process to a severe form and possibly to a fatal outcome [19].

The natural host of LASV is a small rodent named Mastomys natalensis, also called the multimammate rat. The rat is a small soft furred rodent commonly found in West Africa [20]. The virus is transmitted to man by direct contact with the excreta or urine of the carrier rat [7,13].

Presenting Features

Lassa fever in its early stage presents insidiously with symptoms that are usually observed in influenza and some common tropical fevers such as malaria and typhoid fever [21]. In the majority of cases LF manifests as a mild disease [3,13]. Headaches, fever, tiredness, myalgias, are the initial common symptoms corresponding to early viraemia. As the illness gets more serious diarrhea, vomiting of blood, passage of bloody stools, abdominal pain, and skin rash develop, pointing to the onset of gastrointestinal bleeding. Such patients may additionally bleed from mucous membranes of the body, gums, eyes, and nostrils [22-24]. Other clinical features are generalized oedema, deafness, respiratory distress and hypotension. Symptoms referable to the neuronal system include: tremors, deafness, and encephalitis [3,25]. In fatal cases, cardiovascular shock and multi-organ failure may precede death.

Diagnosis

The World Health Organization (WHO) has provided diagnostic criteria for the diagnosis of LF. Essentially where an individual is suspected of having LF, treatment with antimalarials and antibiotics is first offered. If fever persists 48-72 hours after treatment, specific laboratory tests for LF will then be carried out to confirm or rule out a diagnosis of LF.

The laboratory diagnosis is made by ELISA test for LASV antigen or IgM immunoglobin [23,26,27]. The gold standard confirmatory test is by Reverse transcription polymerase chain reaction (RT-PCR) [28-30]. Culture methods have been developed but not commonly available.

Clinical Management

The clinical management of LF entails identification, isolation and barrier nursing of confirmed cases with observance of universal safety precautions by health personnel 31. Whereas there is specific licensed chemotherapeutic agent for LF patients, there is currently no licensed prophylactic vaccine and prevention relies chiefly on public health education and hospital training programs to prevent the nosocomial spread of the infection [31,32].

Intravenous ribavirin is prescribed as soon as LF is confirmed. However oral ribavirin may be offered to suspected cases with a positive history of exposure to or contact with a LF patient. Ribavirin administered intravenously early in the course of LF has proven efficacy but the efficacy of post-exposure prophylaxis with orally administered ribavirin has not yet been confirmed by any properly conducted study [5].

Should the definitive test for LF on a suspected case already on oral ribavirin turn out to be negative, prophylaxis with Ribavirin for the contacts is discontinued. On the other hand should such persons taking oral Ribavirin based on exposure to an LF patient or suspicion develop full blown symptoms of LF, they should urgently be tested for LF by the more sensitive laboratory method, reverse-transcriptase PCR test; and chemotherapy with the intravenous form of Ribavirin started in place of oral ribavirin [33].

Ribavirin

Ribavirin is 1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide. It is a nucleotide analogue of guanosine. It exhibits broad antiviral activity against varieties of RNA and DNA viruses. It effectively suppresses the

proliferation of LASV in vitro but its efficacy in suppressing viremia in vivo is moderate. It causes large decline in the serum levels of aminotransferases (Alanine transferase and aspartate transferase) and significant reduction in cell damage [34].

There have been a number of mechanisms of action proposed, in peer reviewed literature, for its pharmacological actions [35]. Ribavirin is held to be an immunomodulatory agent that up-regulates some specific interferon-stimulated genes and also improves the adaptive antiviral immune response [36-39]. Ribavirin also produces a malfunctioning of the cellular enzyme IMP dehydrogenase (IMPDH) with resultant depletion of GTP (Guanosine triphosphate) and halting of viral replication [40]. Direct inhibition of viral RNA-dependent RNA polymerases, modulation of the host immune response, inhibition of viral capping enzymes, and lethal mutagenesis have also been attributed to Ribavirin [33].

The absolute oral bioavailability of ribavirin increases by 45% to 64% with high-fat diets but decreases when administered concurrently with antacids [41]. Plasma protein binding is small, it has large volume of distribution, and cerebrospinal fluid levels are up to 70% of its plasma concentration. Ribavirin elimination is mainly via the urine; so, clearance is reduced in patients with creatinine clearance less than 30mL/min [41]. Ribavirin greatly improves survival out come in the mouse model of Lassa fever infection when given as a combination therapy with Favipiravir, a direct-acting antiviral agent [34].

Precautions

The use of personal protective equipment including gloves, gowns, masks and goggles is effective in prevention of transmission of highly infectious viruses. Information on highly infectious diseases and education in suitable infection prevention measures should not be limited to healthcare workers, but should also include other professionals such as undertakers or cleaning staff who could potentially be affected and then in turn become sources of transmission of the virus to other people [42].

Antiviral Agents and Prospects for Effective and Safe Vaccines

Although the risk of outbreaks of viral haemorrhagic fevers including LF in various regions of the world has continued to be a significant threat to public health, and despite the enormous burden of Lassa viral haemorrhagic fever in the various affected nations there are still no approved vaccines for LF to date [14,43]. Development and licensing of more efficacious and safe drugs for treatment and effective vaccines to prevent LF are therefore a paramount need of the hour.

With respect to treatment, over the years, supportive clinical measures and the administration of Ribavirin have been the mainstay of therapeutic interventions for LF, however, based on successes recorded on animal models, the direct acting antiviral drug Fevipiravir appears to be a more promising treatment for LF. [44,45] Monoclonal antibodies for LF treatment have also been shown to be effective when introduced early in the course of the disease in animal models (guinea pigs and non-human primates) of LF [46,47].

Presently, number of vaccine candidates for LF is at various stages of drug development [48]. Most of these are replication-competent lassa virus vaccine modalities including the following candidate vaccine platforms: ML 29 which is a reassortment virus generated from combination of the non-pathogenic L-RNA from MOPV (Mopeia virus) and the CS_RNA from Lassa virus Josiah [49,50]; Vaccinia virus vaccine platform [51,52]; the recombinant vesicular stomatitis virus vaccine platform which has proved to be a promising vaccine development effort [53,54]; and Recombinant yellow fever vaccine platform (YFV17D) which is a recombinant vaccine employing the yellow fever 17D vaccine [55,56]. Trials of the recombinant vaccine virus platforms in animal models of LASV have yielded promising results while the recombinant VSV-LASV-GPC vaccine has been found to be safe and effective but requires further trials in human beings [57,58,43].

A novel investigational vaccine named LASSARAB has also been found to be very effective in protecting rats and guinea pigs from both LF and rabies. It is an inactivated recombinant vaccine candidate consisting essentially of an attenuated rabies virus carrier with LASV genetic material inserted into it by the research teams that developed it. Preclinical trials results have been very promising with LASSARAB giving rise to antibodies against both rabies and LF in rodent models when administered with an immune response stimulating protein (GLA-SE adjuvant) [59].

Conclusion

LF has become a major public health challenge. Considering the recurring outbreaks of this virus infection in West Africa, and the attendant socioeconomic burden and loss of lives in the affected nations, development and

licensing of effective and safe vaccines for it have become urgent imperatives.

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