

Countermeasures to Address the Ebola Virus (EBOV) Threat

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Abstract

Ebola virus (EBOV) infects both human and non-human primates (NHP). There are several different EBOV species known that cause severe hemorrhagic disease having very high fatality rates ranging from 25-90%. On March 21, 2014, the Guinea Ministry of Health reported the outbreak of an EBOV-like illness among 49 persons and the Zaire species of EBOV (ZEBOV) was confirmed by polymerase chain reaction and by viral sequencing. Since this discovery the number of ZEBOV cases in Western Africa has risen sharply and now afflicts over >2000 patients and the outbreak worsens. Development of novel countermeasures targeting EBOV is urgently needed as there are no approved vaccines while some therapeutic antiviral countermeasures are being approved for very limited application. With no tools in the toolbox, the measures to contain EBOV rely on isolating patients, identifying their family and contacts, and trying to provide supportive care. This editorial provides an overview of the EBOV problem and discusses some of the current options for countermeasures.

Keywords: Ebola; EBOV; ZEBOV; Counter measures, Antiviral

Introduction

A recent Ebola virus (EBOV) outbreak has stunned the World and now claimed >2000 lives in western Africa [1,2]. EBOV has caused substantial disease in Sierra Leone, Guinea, and Liberia, and has spread to Nigeria [2]. There have been several cases of infected people evacuated to Spain and the United States [3]. As this virus spreads, the world looks to a cure and for countermeasures to control disease. EBV was originally identified in Zaire which is now called the Democratic Republic of Congo [4,5]. The virus was named after the Ebola River in Zaire (ZEBOV), and a minor variant of this strain appears to be the most clinically relevant today having 97% homology to ZEBOV [6].

EBOV is a RNA virus in the filovirus family which has several species including Sudan EBOV, Bundibugyo EBOV, Tai Forest EBOV, and Reston EBOV [7]. These viruses are zoonotic pathogens, a feature that may help explain the historical intermittent circulation among humans. It is unlikely that EBOV will establish in the United States in part because the U.S. lacks some of the animal species that are carriers, and because the Centers for Disease Control and related agencies have the ability to rapidly detect, diagnose, contain and support infected patients [3]. This process proved effective to control other emerging viruses such as SARS coronavirus [8,9]. However, countermeasures and a cure for EBOV are needed.

Vaccination is the primary control strategy for most infectious diseases of humans; however, no licensed EBOV vaccine is currently available. The majority of attempts to generate safe and effective EBOV vaccines resulted in protective immunity in mouse and guinea pig models, but these strategies did not successfully transfer to protecting normal human primates (NHPs) from lethal challenge with EBOV [10,11]. There has been some effort to develop effective therapeutic treatments for EBOV; unfortunately, these have had limited success. The discovery process for EBOV antiviral compounds is also hampered by the requirement to perform the studies with live virus at biosafety level 4 (BSL4). The progress in developing alternative drug screening strategies, such as the use of VLPs, pseudotyped viruses, and minigenomes has facilitated a level of drug screening in a high-throughput manner at reduced lab containment level, i.e. BSL2. Recently, an unlicensed therapeutic has been used and is being considered as a stop-gap measure to save lives. This therapy involved administration of cocktail of humanized-mouse antibodies (ZMapp)

which showed a level of in two U.S. citizens evacuated from Liberia because of EBV disease [12]. Zmapp is manufactured in tobacco plants. The drug is still in experimental stages of development, and it remains unknown as to whether it is safe and effective or not [13].

There are a variety of other therapeutic countermeasures being considered [14]. One example is development of RNA interference (RNAi) lipid nanoparticles to be used as a therapeutic approach for ZEBOV and related EBOVs [15]. This drug when tested in NHPs who were infected with ZEBOV protected from death. Another experimental therapeutic is a modified RNA molecule that targets VP24 of ZEBOV to prevent its expression [16]. The drug tested in pre-clinical trials on ZEBOV-infected NHPs has a reported cure rate of 60 to 80 percent. Similarly, there are a number of unapproved EBOV vaccines that industry is working on. Several laboratories are working on an adenovirus vectored vaccines [17]. For example, one group is developing a chimpanzee adenovirus vector engineered to express two ZEBOV proteins [18]. Preliminary data has shown the vaccine generates a favorable immune response in pre-clinical trials on NHPs. There is also several vaccines based on attenuated recombinant vesicular stomatitis virus (rVSV) vectors against EBOV [19-21]. These vaccine constructs have shown promising results in preclinical trials, where using one dose has been shown to be effective to protect guinea pigs and NHPs against ZEBOV [20]. In addition, DNA and virus-like particle (VLP) vaccines are being considered [22,23]. In preclinical trials, DNA vaccines have been effective at induced robust immune responses and elicited 100% protection against a challenge with different strains of EBOV in two different animal models [22].

In the end, there are currently no safe and approved countermeasures for EBOV, a virus that can be spread by respiratory droplets and by

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direct contact with infected body fluids. It is critical that antivirals be developed. Building from the availability of the EBOV genome sequences, and our understanding of the virus replication cycle, is one path forward in the development of novel vaccine and therapeutic approaches, including the use of 'reverse vaccinology' to develop logical vaccines. Additionally, future EBOV research should focus on understanding the virus-host interface to better understand the cellular processes involved in EBOV replication and pathogenesis. In this regard it will be important using to use existing '-omics' approaches that include deep sequencing, broader genomics and proteomics approaches, and generate constructs that allow for investigation in BSL2 laboratories. Critical to meeting the goals will be transparent communication and being able to effectively combine data obtained in the same and related experimental settings.

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