SCIENTIFIC FEDERATION
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Manoj Kumar Sarangi, SF Drug Deliv Res J, 2017, 1:1

SciFed Drug Delivery Research Journal

Review Article Open Access

Ebola Infection, Its Prevention as Well as Therapeutic Measures

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Abstract

Ebola virus is propagated to people in a result of direct contact with body fluids containing virus of an infected patient. The incubation period usually lasts 5 to 7 days and approximately 95% of the patients appear signs within 21 days after exposure. Typical features include fever, weakness, diarrhea, cramping, nausea, abdominal pain and vomiting for 3-5 days and maybe persisting for up to a week. Laboratory complications including enhanced aminotransferase levels, marked thrombocytopenia and lymphocytopenia may have occurred. The symptoms progress over the time and patients suffer from dehydration, stupor, confusion, hypotension, multi-organ failure, leading to fulminant shock and eventually death. The most general assays used for antibody detection are direct IgM ELISA's and IgG and IgMcapture ELISA. Continued focus on strengthening clinical and public health infrastructure will have direct benefits in controlling the spread of EVD and will provide a strong foundation for deployment of new drugs and vaccines to affected countries when they become available. The unprecedented West Africa Ebola outbreak, response measures, and ensuing vaccine and drug development suggest that new tools for Ebola control may be available in the near future.

Keywords

Ebola; Thrombocytopenia; Elisa; nausea; hypotension

Introduction

Ebola hemorrhagic fever (EHF) is defined as an acute viral syndrome which comprises with fever along with an intense bleeding diathesis which is a cause of high mortality in both human as well as non-human primates. It is caused by Ebola virus, a lipid-enveloped, negatively stranded RNA virus that belongs to the viral family Filoviridae (World Health Organization 1997). The first Ebola fever cases were reported during 2 simultaneous outbreaks in both southern Sudan and the Democratic Republic of Congo (formerly Zaire) [1]. Fatality rates reached 53% and 88%, respectively (Klenk and others 1995; Centers for Disease Control and Prevention [CDC] Special Pathogens. From that time until January 2003, 10 significant Ebola fever outbreaks have occurred in Africa involving more than 1600 cases of infection and 1100 fatalities. In addition, there have been a small number of subclinical infections in the United States and the Philippines from the Reston strain of the virus, which is harmless to humans but lethal for monkeys (CDC Special Pathogens Branch 2002b). Irrespective of concerted investigative efforts, the natural reservoir of the virus is not known, thus a very little is understood about how Ebola virus replicates in its host as well as how it is transmitted.

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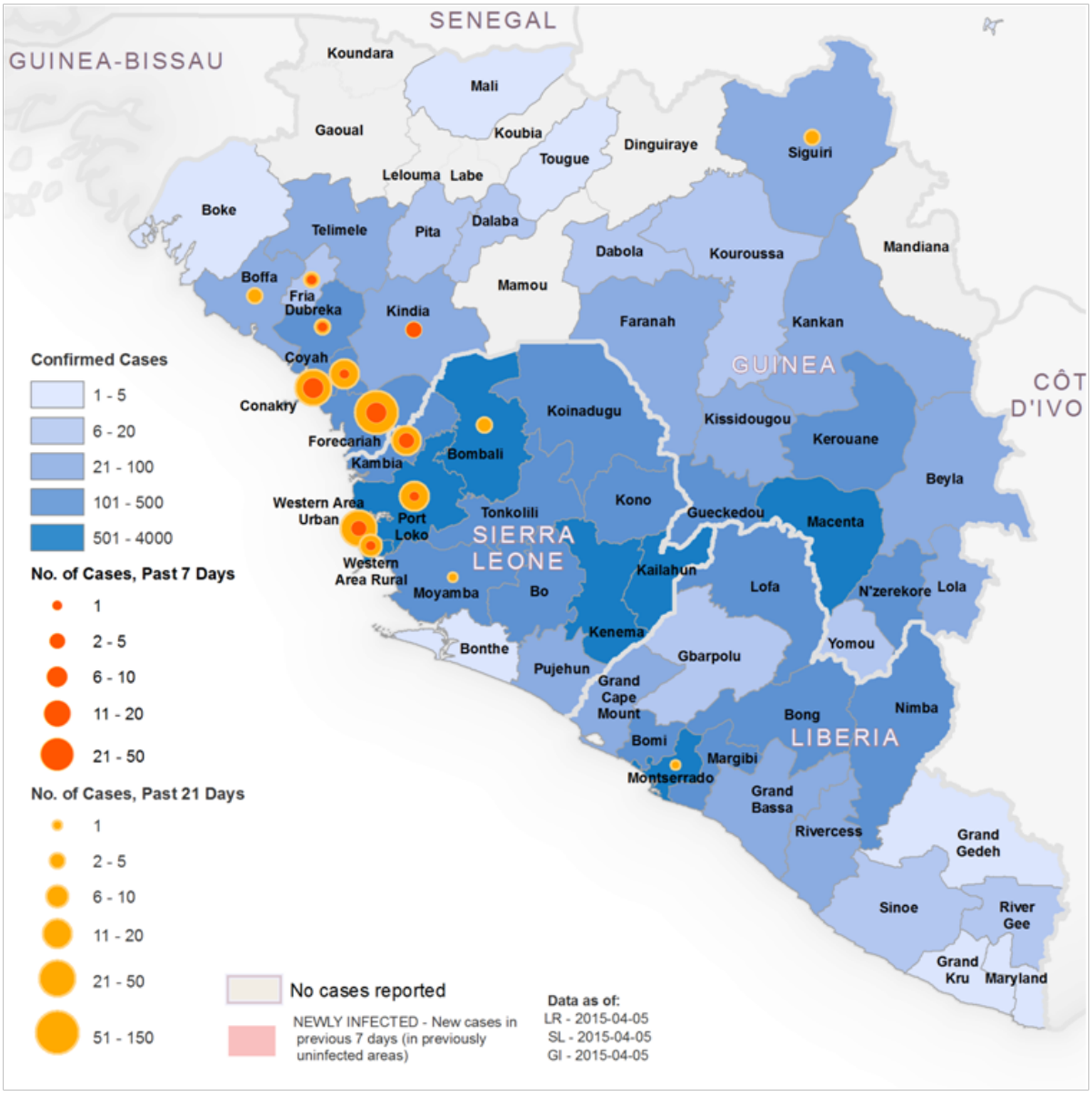
Received July 28, 2017; **Accepted** September 2, 2017; **Published** September 30, 2017

Citation: Manoj Kumar Sarangi (2017) Ebola Infection, Its Prevention as Well as Therapeutic Measures. SF Drug Deliv Res J 1:1.

However, based on evidence from similar viruses, it is theorized that the virus is zoonotic and therefore is maintained by an unidentified animal host (Peters and LeDuc 1999; World Health Organization 2000; CDC Special Pathogens Branch 2002b). The fact that outbreaks of EHF have coincided with the end of the African rainy season may provide a clue to the natural ecology of Ebola virus and to the host, which may be influenced by this weather cycle [1].

Ebola viruses from Africa cause Infections with a more severe disease in humans, which is named as Ebola virus disease (EVD). Five different species of the genus Ebola virus (Filoviridae family) have been identified from different samples collected from non-human and human primates during the outbreaks of the disease: Since the first documented EVD outbreak in Zaire (now: the Democratic Republic of Congo) in 1976 in locations like Zaire ebolavirus (EBOV), Sudan ebolavirus, Reston ebolavirus, Taï Forest ebolavirus and Bundibugyoebolavirus [2]. Ebola viruses and Marburg virus, another member of the Filoviridae family, are classified as biosafety level 4 pathogens (BSL-4; risk group 4) which requires a very special containment measures and barrier protection, especially for healthcare workers.

Figure 1: Distribution of Ebola virus disease outbreaks in Africa



Structure and Classification of the Ebola virus

Ebola viruses along with the related Marburg virus are members of the Filovirus family, which are pleomorphic, negative-sense RNA viruses whose genome organization is most similar to the Paramyxoviridae. Amongst the four identified strains of Ebola virus, three i.eIvory Coast, the Zaire, and Sudan strains have been shown to cause disease in both humans as well as nonhuman primates, with the Zaire strain exhibiting the highest lethality rate [3, 4]. The only documented outbreaks of Ebola virus infection in the United States were fortunately restricted to nonhuman primates at holding facilities in Virginia and Texas, caused by the Reston strain, which has not yet caused fatal disease in humans [5]. The length of Ebola virus genome is 19 kb, with seven open reading frames encoding structural proteins, including the virion envelope glycoprotein (GP), nucleoprotein (NP), and matrix proteins VP24 and VP40; nonstructural proteins, including VP30 and VP35;and the viral polymerase (reviewed in reference 28). Just like that of Marburg virus, the GP open reading frame of Ebola virus gives rise to two gene products, a soluble 60- to 70-kDa protein (sGP) and a full-length 150- to 170-kDa protein (GP) that inserts into the viral membrane [4, 6] through tranblockedional editing.

Pathogenesis and Transmission

Typically, Ebola virus infection runs its course within 14 to 21 days. However the Infection is initially associated with nonspecific flu-like symptoms such as myalgia, fever, and malaise. With progresses of the infection, the patients exhibit severe abnormalities like bleeding and coagulation, along with gastrointestinal bleeding, rash, and hematological irregularities, like neutrophilia and lymphopenia. Cytokines gets released as and when reticuloendothelial cells encounter virus, which is associated with exaggerated inflammatory responses which are not protective. The damage associated with liver, in combination with massive viremia, results with disseminated intravascular coagulopathy. The virus thus infects micro vascular endothelial cells and compromises with vascular integrity. The terminal stages of Ebola virus infection usually is associated with hypertensive shock and diffuse bleeding thus accounts for many Ebola virus fatalities [7, 8].

The infection generally involves necrosis of the liver, spleen, kidney, lymph nodes, testes, and ovaries due to viral replication within parenchymal cells. More significant effects are micro vascular damage, changes in vascular permeability, and activation of the clotting cascade. Damage to platelets and endothelial cells results in the disruption of fluid balance and homeostasis. In addition, the virus is believed to compromise and suppress immunological function [1]. Though the primary source of infection is not known, but the epidemiologic mode of transmission is well defined. Ebola fever outbreaks among humans begin with an index case that is subsequently transmitted to secondary individuals by close, intimate contact with blood, body secretions, excretions, organ tissue, or semen; nosocomial infection precipitated by the reuse of unsterilized syringes and failure to follow the universal precautions of barrier nursing; or unhygienic practices, such as unsterile burial customs involving the rigorous external and internal cleansing of an infected corpse. The main routes of infection are through mucous membranes, the conjunctiva, and small skin. Case reports of hospital personnel acquiring the disease that are not attributable to the percutaneous route suggest that rubbing one's eye after caring for a patient with acute illness transmits enough inoculums to produce clinical infection. Aerosol dissemination of Ebola virus has not been established as a mode of transmission in humans. However, in nonhuman primates, this mode of transmission has been associated with disease [1]. There is no evidence of communicability during the viral incubation period with no febrile, asymptomatic individuals (World Health Organization 1997). Isolated cases of transmission between individuals convalescing from EHF and close household contacts have been found and are primarily attributed to sexual contact. Rowe's (1999) cohort prospective study described a case involving a male convalescent who had Ebola viral antigen still present in seminal fluid almost 3months after the initial diagnosis. Transmission risk does increase significantly with direct patient contact during the acute disease phase [1].

Clinical Presentation and Diagnosis

Incubation ranges from 2 to 21 days. The variable clinical presentation of Ebola fever can make differential diagnosis difficult. Early symptoms may resemble influenza, malaria, typhoid fever, fulminant hepatitis, sepsis, nontyphoidal salmonellosis, and various forms of encephalitis, dengue fever, yellow fever, Lassa fever, Marburg, and other hemorrhagic diseases. Perplexing noninfectious syndromes with hemorrhage such as lupus erythematosus, acute leukemia, hemolytic uremic syndrome, and idiopathic or thrombotic thrombocytopenia

purpuraalso fall into the differential diagnosis. Thus, clinical diagnosis is presumptive until there is laboratory confirmation of Ebola virus. Typically, the onset of Ebola fever is sudden, with most cases presenting in 5 to 12 days. The clinical symptoms begin with a nonspecific prodrome. Early symptoms can include acute fever, chills, myalgia, headache, arthralgia, and anorexia. Nausea, vomiting, abdominal pain, hypotension, tachypnea, relative bradycardia, conjunctivitis, conjunctival injection, pharyngitis, and diarrhea, which may be bloody, are other evolving signs. Cutaneous flushing or prominent, nonpruritic, maculopapular centripetal rash are common. Infected women who are pregnant frequently abort. Dehydration and wasting are present as the disease advances. Later, the illness may develop into a progressive hemorrhagic diathesis that features epistaxis, hematuria, hematemesis, petechiae, melena, and mucous membrane and conjunctival hemorrhage. Hemorrhaging usually occurs from the gastrointestinal tract, lungs, and gingiva. As the vascular bed is the main target of Ebola virus, disseminated intravascular coagulation (DIC) becomes the dominant clinical feature. Abnormal laboratory findings typically indicate leukopenia with a left shift, atypical lymphocytes, thrombocytopenia, elevated transaminase levels, hyperproteinemia, proteinuria, hematuria, and prolonged bleeding time, prothombin time, and activated partial thromboplastin time [1]. There may be central nervous system involvement that results in delirium, somnolence, or convulsions. These symptoms, in addition to DIC, are indicative of poor prognosis. Patients who are going to develop immune response against the virus will begin to recover within 7 to 10 days and thus start a period of slow as well as prolonged convalescence associated with complications such as hepatitis, uveitis, weakness, fatigue, and other clinical Conditions. Patients who do not improve by the 1st week usually experience multi organ failure and die from hypovolemic shock, with or without blood loss.

Options for prevention and control

Prevention of infection for tourists, visitors and residents

The risk of infection is considered to be very low for tourists, visitors or residents in affected areas if some elementary precautions are followed:

• By avoiding the contact with symptomatic patients as well as their bodily fluids

• By avoiding the contact with corpses as well as bodily fluids from deceased patients

In addition to the above, the generic precautions for travelling in various West African countries are also applied in order to prevent the infection with Ebola virus:

• By avoiding close contact with wild animals of any form (including rodents, bats monkeys and forest antelopes), both dead and alive, and consumption of any kind of 'bush meat'

• peeling and Washing vegetables and fruits before consumption

• practicing 'safe sex' very strictly

• Following hand-washing routines very strictly

It is very strictly instructed to avoid the areas which are highly populated by bats such as caves, mining sites or isolated shelters.

Prevention for healthcare workers

In healthcare settings, the risk level can vary from very low to low. However, it has been observed that, the risk is of very high in the event of mishaps which results in mucosal exposure or skin penetrations of contaminated materials (e.g. needle stick injuries).

Preventive approaches for healthcare workers include:

• Full acquiescence to malaria prophylaxis and vaccinations (notably yellow fever) as they are highly recommended for the target sites. (including documentation as a vaccination record)

• Sensitization for viral hemorrhagic fever symptoms are highly recommended before working in endemic countries; and Strict enactment of barrier management, use of disinfection procedures and personal protective equipment as per the guidelines [2].

Patients and healthcare workers are very much prone to be exposed to an unrecognized Ebola patient. Thus Unrecognized Ebola virus fever is having a high potential for spreading within a healthcare setting. This is caused by possible exposure to bodily fluids as well as close interpersonal contacts which are occurring during

diagnostic, nursing and treatment procedures, including the manipulation of biological samples. Depending on the conditions of an undiagnosed patient, the risk for other patients and/or healthcare workers may rise to 'moderate' or 'high'. The minimization of lag time for suspecting as well as diagnosing EVD in a symptomatic patient is much more essential for having the outbreaks in a healthcare system. Once a case of EVD is suspected, the procedures in the healthcare facility are carried out very strictly even though the EVD was already confirmed. The responses include:

• Contact tracing among staff and patients who have been in contact with the suspected patient

• Medical monitoring of identified contacts (fever and prodromal symptoms)

• Immediate notification of the competent public health authorities

• Improvised barrier management in all areas where the suspected patient has been treated (contaminated zone, transition or sluicing zone, 'clean' zone)

• Patient handling under droplet hygiene precautions; in case of invasive, potentially aerosol-generating procedures: airborne transmission precautions

• Retaining waste and any type of bodily fluids from the patient in the contaminated zone until appropriate decontamination and disposal provisions are in place

• Handling and shipment of patient samples according to the international procedures for 'transport of category an infectious substance assigned to UN 2814 or UN 2900' [2]. Hospital preparedness measures promoting early detection and safe handling of viral hemorrhagic fever cases:

• Sensitization of staff working in 'ports of entry' in a healthcare setting (emergency departments, ambulance services, GP offices) for early and advanced symptoms of viral hemorrhagic fever

• Focusing on systematic recording of travel history and vaccinations received

• Establishing a standard diagnostic procedure for ruling out common differential diagnoses at an early stage (e.g. malaria, yellow fever, dengue, Lassa fever, rickettsia and leptospirosis)

• Establishing a protocol for notification of the competent public health authorities at an early stage if suspecting an EVD case

• Knowing of, and establishing contact to, reference laboratories able to perform viral hemorrhagic fever diagnostics

• Knowing of, and establishing contact to, specialized treatment centers with high containment facilities

• Delivering basic training to healthcare workers on principles of provisional barrier nursing and use of personal protective equipment for droplet transmission precaution

Vaccine Development

Several animal models have been developed to study the pathogenesis of Ebola virus infection and to assess the efficacy of various vaccine approaches. As the progression and pathogenesis of the disease is most closely resemble with those of the human disease conditions hence, Guinea pigs and nonhuman primates represent the primary animal models for vaccine development [9, 10, 11]. However a murine model was developed later on with serial passage of virus in mice [12]. In spite of using the model for knockout and inbred strains to evaluate genetic determinants of disease, however, it is also considered to be very less predictive of human disease as because it is dealing with a serially pass aged, attenuated virus. Though the symptoms and time of course of the disease in guinea pigs gets paralleled to those in humans but still the nonhuman primate infection is considered to be the most predictive as well as useful for vaccine development[13]. Recombinant proteins and live attenuated viruses have been used successfully in developing a variety of vaccines, but however the immunogenicity and safety of gene-based vaccines have proven much more attractive. However naked plasmid DNA among the gene-based approaches has been used successfully in animal models in order to direct the synthesis of immunogens within the host cells and thus has been found helpful in a variety of infectious diseases. Genetic immunization along with plasmid DNA was the first successful vaccine for Ebola virus developed in the guinea pig [11]. In this model, sGP and GP elicited

T-cell proliferative and cytotoxic responses as well as a humoral response whereas NP elicited a primarily humoral response and was less efficacious. The Protection against lethal challenge was confirmed by each of these immunogens while animals get infected within 1 month of the last immunization, but however only GP or sGP have provided the long-lasting protection. The degree of protection is associated with antigen-specific T-cell responses and antibody titer. However the Subsequent studies based on NP and GP plasmids conferred a protective immunity in mice [14], but it is very much uncertain that whether the attenuated murine virus is found to be more sensitive to neutralization than the wild-type virus. Hence, the usual potency of NP, or its requirement as an immunogenic for developing long-term protection, remains uncertain. However the DNA vaccines have been highly effective in rodents and their efficacy in nonhuman primates or humans are very less impressive. Priming-boosting immunization protocols that can use DNA immunization followed by boosting with poxvirus vectors have carried out the genes for pathogen proteins which have yielded dramatically enhanced immune responses in animal studies along with 30- fold or greater increase in antibody titer from that of the booster [15]. Thus a different priming-boosting strategy along with replication defective adenovirus for an Ebola virus vaccine was tested in cynomolgus macaques [16]. Hence the above study represented a superior immunologic efficacy of this priming-boosting combination towards both humor land cellular responses. The animals have displayed a complete immune protection against a lethal challenge of virus by providing a first and foremost demonstration of an Ebola virus vaccine approach which protects the primates against infection. Recently, an accelerated vaccination has been designed which confers a protection against the lethal virus challenge in several nonhuman primates with a single immunization [17]. If this vaccine works in a similar fashion in humans, it would be very useful in the containment of acute outbreaks through ring vaccination. Thus in brief, an understanding of the mechanisms associated with Ebola virus-induced cytopathic effects has prorogued the process of vaccine and antiviral therapy development, which in fact provided novel information about pathogenesis and the immune response. It has been observed that Ebola virus does not exhibit the high degree of variability just like other enveloped viruses which may employ to evade host immunity, however the Ebola virus GP can alter the target-cell function and thus exemplifies a novel strategy for immune evasion which may have been developed through the evolution of the dangerous Ebola virus with its natural host. The cytotoxic effects of GP on macrophage and endothelial cell function leads to disrupt inflammatory cell function as well as the integrity of the vasculature. Ebola virus can disrupt the processes associated with critical immune activation and cytolytic-T-cell function by altering the cell surface expression of adhesive proteins and immune recognition molecules. These phenomena are having the accountability for the deregulation of the vascular dysfunction characteristic of lethal Ebola virus infections well as the inflammatory response and providing a region for focusing on GP as a target for a preventative vaccine, thus providing a lead for other clinical interventions.

Plants as a production platform for antibodies

Plants have been used as bioreactors for antibody production as they offer several potential advantages over other conventional production systems, including using bacteria, yeast or mammalian cell culture [18]. Plant production facilities are cheaper than equivalent bioreactors, and offer a rapid gene to protein turnaround time and high scalability. They are not susceptible to contamination with mammalian-tropic pathogens. Post-translational modification (PTM) in plants is controllable [19] and represents an important advantage over using bacteria since many proteins, including most antibody formats, do not fold correctly and have limited functionality when expressed without PTM.

To produce antibodies in plants, plants must be transformed with genes encoding antibody proteins. Typically, the bacterium Agro bacterium tumefactions is used to transfer recombinant regions of DNA encoding for the genes of interest into the plant nucleus through the activity of the virus (virulence) operon. These DNA regions are termed transfer DNAs (T-DNA). T-DNA is capable of integrating into plant chromosomes, generating a stable transgenic cell that can be regenerated into a whole plant. However, a high level of tranblockedional activity occurs before integration takes place. This burst of tranblockedion can be utilized to produce large amounts of recombinant protein without the need for time-consuming regeneration steps. Furthermore, the rate of tranblockedion can be significantly enhanced through the simultaneous delivery of viral genes encoding proteins directing the replication of RNA or even permitting cell-to-cell spread of message [20].

A comparison of these two plant-based approaches with other methods of producing recombinant proteins is provided in Table 2. Crucially, transient expression allows antibodies to be expressed with faithful PTMs at scale and within an extremely short time frame, without the need for expensive bioreactors or product-dedicated production facilities. Transgenic plants require no specialized equipment for growth or antibody production except that required for the control of genetically modified organisms and can be grown at agricultural scale. Downstream processing is similar for both approaches, and protein A or G matrices are commonly used to purify mAbsfrom plant extracts.

Plant mAbs for Ebola

Following the isolation of protective mAbs against epitopes on Ebola glycoprotein [21], Mapp biopharmaceutical Inc. reengineered the sequences for expression via A. tumefaciens mediated T-DNA transfer to N. benthamiana plants. Ebola 6D8 mAb was produced in leaves using an expression cassette based on the ssDNA virus Bean Yellow Dwarf Virus, a geminivirus [22]. The 6D8 mAb, against Ebola GP1 protein, was produced at 0.5 mg of mAb per gram of leaf fresh weight within 4 days, which is considered a high yield and compares well with other production approaches (CHO cells typically yield up to 10mg/l culture volume). Zeitlin et al. produced 13F6 mAb in plants and investigated the influence of the plant N-glycan in the Fc region [23]. It was found that the plant glycan was associated with improved protective efficacy compared with mammalian (CHO cell) glycans, and antibody-dependent cellular cytotoxicity (ADCC) was implicated as an important mode of action for this antibody.

Antibody Cocktails

Two significant drawbacks to the use of antibody monotherapy in the treatment of infectious disease are incomplete coverage of circulating strains and the emergence of escape mutants that are no longer sensitive to neutralization. To avoid these shortcomings, it is preferable that a combination of antibodies recognizing different epitopes is used as an immunotherapy. In a pivotal study concerning the antibodies produced by Mapp biopharmaceutical Inc., Olinger, et al. compared the protective efficacy of humanized mAbs 13C6, 13F6, and 6D8, produced from CHO cells and plants (N. benthamiana) and the mixture of these three mAbs (MB-003) in rhesus macaques [24]. Thus from the above study we came to a conclusion that MB-003 produced from both plants and CHO cells can protects rhesus macaques from lethal EBOV challenge while administered 1 hour after the infection. Moreover, the animals showed little viremia and few clinical symptoms.

Pettitt, et al. demonstrated that the MB-003 prevented death in 43 % of rhesus macaques from EBOV infection after appropriate diagnostic indicators became positive, whereas all the untreated animals succumbed to the infection [25]. This study was important, as previous work has focused on pre-exposure treatment or treatment within a short window after infection, which is not an appropriate model for EBOV infection in a developing country outbreak scenario. This study ultimately paved the way for the use of the ZMapp™ antibody cocktail in infected humans. ZMapp™ is a cocktail of three antibodies, including at least one of the components of MB-003, and at least one of the antibodies isolated by Qiu et al. and commercialized by Defyrus Inc. of Canada (ZMab). Limited information is available on the ZMapp™ cocktail although it has shown efficacy in the non-human primate challenge model and Mapp Biopharmaceutical Inc. will shortly publish these data (K. Whaley, pers. comm.). All component antibodies are believed to bind EBOV GP. Licenses to develop both sets of antibodies have been granted to Leaf Biopharmaceutical Inc., the commercialization partner of Mapp Biopharmaceutical Inc., who has made a limited supply of ZMapp™ available at no cost. The production of ZMapp™ has also been scaled up to supply those with a legitimate need for the experiment therapy, and to demonstrate the potential of transient expression platform to provide a cost effective rapid response system to meet global health challenges of emerging pathogens.

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Citation: Manoj Kumar Sarangi (2017) Ebola Infection, Its Prevention as Well as Therapeutic Measures. SF Drug Deliv Res J 1:1.