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“An Outbreak Is Needed For Ebola Virus Treatment” A Review



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ABSTRACT

Ebola virus causes acute hemorrhagic fever in humans and non-human primates. Ebola virus constitutes an important local public health threat in Africa, with worldwide effect through imported infections and through the fear of misuse for biological terrorism. 2014 outbreak of Ebola virus hemorrhagic fever has 90% fatality rate, with no prophylaxis or treatment available. Lack of pre and post-exposure interventions makes the development of rapid diagnostics, new antiviral agents and protective vaccines a priority for many nations.



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INTRODUCTION

Ebola Virus disease (EBOV) was isolated in 1976 in Zaire and Sudan – simultaneously. The name Ebola originates from Ebola River where the first sets of cases were isolated. It is not airborne, and the only means of transmission is close contact with the body fluids of non-primates. The advent of the disease has spread across the frontiers of continents. Ebola virus belongs to the family Filoviridae¹. There are five known species of Ebola virus: Bundibugyo Ebola virus (BDBV), Zaire Ebola virus (EBOV), Reston Ebola Virus (RESTV), Sudan Ebola Virus (SUDV), Taiforest Ebola Virus (TAFV)². EBOV became a threat to public health when it re-emerged in Kikwit, Democratic Republic of Congo, in 1995. This outbreak received much attention from the media and made EBOV one of the most feared infectious agent worldwide. Since the tragic events of 11 September 2001 another dimension was added in bioterrorism.

Programmes to produce large quantities of filoviruses (EBOV and MARV) were carried in the past. Today EBOV is not only feared as most pathogenic human agents but also as an agent that poses a potential bioterrorism threat³. Lack of pre and post-exposure interventions makes the development of rapid diagnostics, new antiviral agents and protective vaccines a priority for many nations. Previous studies of Ebola virus were limited by the biohazards associated with investigations. As attempts are made to develop strain-specific, antibody-dependent enhancement of infection for the extreme virulence of the virus. An issue has arisen to develop an Ebola virus-specific vaccines and the use of passive prophylaxis or therapy with Ebola virus-specific monoclonal antibodies⁴.

ECOLOGY

Ebola virus is a zoonotic pathogen. Intermediary hosts have been reported to be "various species of fruit bats throughout central and sub-Saharan Africa". Evidence of infection in bats has been detected through molecular and serologic means.

SYMPTOMS

Ebola virus disease is characterized by fever, chills, malaise, and myalgia. The subsequent signs and symptoms indicate multisystem involvement and include muscle and joint pain, vomiting, abdominal pain, diarrhea, chest pain, shortness of breath, postural hypotension, oedema,

headache, confusion and unexplained internal and external bleeding manifestations. Hemorrhagic manifestations arise during the peak of the illness and include petechiae, ecchymosed, uncontrolled oozing from venepuncture sites, mucosal hemorrhages^{5,6}.

STRUCTURE

Ebola virus is filamentous, non-segmented, linear RNA genome that is non-infectious and does not contain poly (A) tail. After entry into the cytoplasm of host cell, it is transcribed to generate the polyadenylated subgenomic messenger RNA species.

The genome has the following characteristics gene order: 3`leader, nucleoprotein (NP), Virionprotein 35 (VP35), VP 40, glycoprotein (GP), VP 30, VP 24, Polymerase (L) protein and 5` trailer. Transcription and translation lead to the synthesis of 7 structural polypeptides with presumed identical functions. Four proteins are associated with the virus genomic RNA in the ribonucleoprotein complex: NP, VP30, VP35 and L protein. NP, VP 30 and L are essential and sufficient for transcription. The 3 remaining structural proteins are associated with the membrane⁴.

TREATMENTS

No drug and vaccine had yet been approved by the United States Food and Drug Administration (FDA) for clinical use in humans.

The FDA has established the “animal rule” allowing licensure to be approved on the basis of animal model studies that replicate human disease, combined with evidence of safety and a potentially potent immune response.

Phase I clinical trials were presently carried out by the administration of the vaccine to healthy human subjects to evaluate the immune response, identify any side effects and determine the appropriate dosage and still in the trial.

NEW THERAPEUTICS APPROACHES ON EBOLA VIRUS INFECTION USING MONOCLONAL ANTIBODIES

Monoclonal antibodies are nonspecific antibodies that are made by identical immune cells that are all clones of a unique parent cell, in contrast to polyclonal antibodies which are made from several different immune cells.

The idea of a "magic bullet" was first proposed by Paul Ehrlich, who, at the beginning of the 20th century, postulated that, if a compound could be made that selectively targeted a disease-causing organism

Initially, combination of monoclonal antibodies with interferon- α (a protein that stimulates an antiviral response) provided protection of macaques in Ebola virus challenge. ZMapp, an antibody therapy that does not require interferon- α ^{7,8}. ZMapp was made by testing different combinations of chimera monoclonal antibodies (in which fragments of human antibodies) are attached to antibody fragments from mice.

Successful treatment of Ebola virus-infected cynomolgus macaques with monoclonal antibodies.

Qiu *et al.*, 2013 studied that treatment of the macaques 24 or 48 hours after Ebola virus challenge with a virus-neutralizing antibody cocktail (ZMapp). Surviving macaques developed both Ebola-specific antibodies and T cell responses. Thus passive neutralizing antibody transfer may keep the virus in check long enough for endogenous immunity to take over⁹.

Monoclonal Antibody Treatment and Vaccine Produce Encouraging Results against Ebola Virus

A second international team reported progress with a vaccine. Past research shows that human-derived adenovirus-type vectors containing Ebola virus antigens generate a potentially protective immune response except in the considerable fraction of people who have been exposed to human adenovirus in the past and who consequently have antibodies against human adenovirus vectors. Therefore, the researchers developed a chimpanzee-derived adenovirus vector. In macaques, the

vaccine rapidly induced both acute and durable protection against an Ebola virus challenge given 5 weeks after immunization. In unvaccinated animals, the virus challenge was lethal¹⁰.

Recombinant Human Monoclonal Antibodies to Ebola Virus

Human Fab (IgG1 κ) phage display libraries were constructed from bone marrow RNA from 2 donors who recovered from infection with Ebola (EBO) virus. The libraries were initially planned against a radiation-inactivated EBO virus—infected Vero cell lysate, but only weak binders identified. Planning against secreted EBO glycoprotein (SGP) resulted in Fabs showing very strong reactivity with SGP in ELISA. These Fabs also reacted with a virion membrane preparation. The Fabs were strongly positive in IFAs with cells infected with EBO (subtype Zaire) virus but negative with uninfected cells, with a characteristic punctuate staining pattern in the cytoplasm. The Fabs are now being characterized in structural and functional terms¹¹.

Treatment of Ebola virus infection with plant-derived Monoclonal antibodies:

Olinger *et al.*, 2012 produced three anti-Ebola virus mouse/human chimera mAbs (c13C6, h-13F6, and c6D8) in Chinese hamster ovary and in whole plant (*Nicotiana benthamiana*) cells. A mixture of the three mAbs (MB-003) protected rhesus macaques from lethal challenge¹².

Therapy with Ebola Virus Glycoprotein antibodies:

Takada *et al.*, 2011 treated antisera of mice and guinea pigs by DNA immunization with a plasmid encoding the surface glycoprotein (GP) of the Zaire strain of Ebola virus enhances the infectivity of vesicular stomatitis virus pseudotyped with the GP. Substantially weaker enhancement was observed with antiserum to the GP of the Reston strain, which is much less pathogenic in humans than the Ebola Zaire and Sudan viruses. The enhancing activity was abolished by heat but was increased in the presence of complement system inhibitors and suggested that heat-labile factors other than the complement system are required for the effect. They also generated an anti-Zaire GP monoclonal antibody that enhanced an anti-Zaire GP monoclonal antibody that enhanced viral infectivity and another that neutralized it, indicating the presence of distinct epitopes. Their findings suggested that antibody-dependent enhancement of infectivity may account for the extreme virulence of the virus. They also raise issues about the

development of Ebola virus vaccines and the use of passive prophylaxis or therapy with Ebola virus GP antibodies¹³.

Enhancement of Ebola Virus Infection dependent antibodies:

Takada et. al. 2003 experimentally showed that Ebola Zaire virus infection in humans induces antibodies which enhance viral infectivity. Plasma or serum from convalescing patients enhanced the infection of primate kidney cells by the Zaire virus and the enhancement were mediated by antibodies to the viral glycoprotein and complement component C1q. He suggested a model in which two or more molecules of monomeric IgG antibodies bind to specific GP epitopes in close proximity, allowing C1 to bind to the Fc portion of the antibodies. The resultant complex consists of the virus antibodies and C1 that bind C1q ligands at the cell surface, promoting either binding of the virus to Ebola virus-specific receptors or endocytosis of the target cells by intracellular signaling via C1q ligands¹⁴.

Glycoprotein Specific Monoclonal Antibodies Protect Mice and Guinea pigs from lethal Ebola Virus Infection:

Xiangguo Qiu, et. al., 2012 experimentally proved that the combination of three neutralizing monoclonal antibodies (mAbs) against the Ebola envelope glycoprotein (GP) resultant in complete survival of four cynomolgus macaques with no apparent side effects when three doses were administered 3 days apart beginning at 24 hours after a lethal challenge with EBOV. The same treatment initiated 48 hours after lethal challenge with EBOV resulted in two of four cynomolgus macaques fully recovering. The survivors demonstrated an EBOV-GP-specific humoral and cell-mediated immune response. He suggested that antibodies play an important role in controlling EBOV replication *in vivo*, and supported the use of mAbs against a severe filovirus infection¹⁵.

CONCLUSION

Ebola virus causes rapidly fatal hemorrhagic fever in humans. As there is no specific vaccine for treating Ebola resulting in large number of deaths. Poverty, lack of awareness and human habitats are playing major role in spreading the disease in large scale. So far, the experiments are proved that antibodies played an important role to control EBOV and supported the use of mAbs

for development of EBOV vaccines. Future efforts need to focus on more detailed investigations to control Ebola virus outbreak.

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