Disease Mechanism and Treatment Method of Ebola Virus

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Abstract. Ebola virus is a virus with simple structure, but it can assemble itself in the host and cause a chain reaction of washing in the process of disease causing, leading to more serious pathological damage in the body. Its main clinical characteristic is fever, bleeding, and diarrhea and has a high fatality rate, as well as endangering people's physical and mental health. Since Ebola virus was discovered in 1976, the virus has been in periodic outbreaks in Africa, and has also spread to countries and regions outside the African continent. The World Health Organization has twice listed Ebola as a public health emergency of international concern. In view of the huge challenges faced, the search for effective treatment methods and the research and development of preventive vaccines have become one of the problems that the medical community urgently needs to overcome. Antibody drugs also play an important role to prevent the spread of Ebola virus, improving patient protection rate and other aspects, making people see the hope of curing Ebola virus. So far, the American Food and Drug Administration (FDA) have approved REGN-EB3 and mAb114 as medicinal products for Ebola Virus therapy. This article reviews the risk factors, pathogenesis, clinical characteristics and treatment progress of Ebola virus, to provide a theoretical basis for the prevention and treatment of the virus.

Keywords: Ebola Virus, Disease Mechanism, Treatment.

1. Introduction

Ebola is a fatal disease affecting humans and other primates, such as monkeys, gorillas, and chimpanzees, caused by ebolaviruses. In essence, these viruses are five in number, including Zaire, Sudan, Bundibugyo, Tai Forest, as well, and Reston ebolaviruses. This condition was first reported in the Ebola River in the Democratic Republic of Congo and is prevalent in West African countries. Ebola is characterized by severe inflammation as well as tissue damage to the human body. The common symptoms include fever, bleeding inside and outside the body, diarrhoea as well as body aches. Ebola is a highly contiguous as well as fatal disease whose disease mechanism has to be explored, and the prevention, as well as treatment measures to help reduce its mortality rate. Humans contract the Ebolavirus (BOV) from wild animals, and it then spreads from one person to another. Fever, headache, weariness, muscular aches, internal and external bleeding, diarrhoea, vomiting, and impaired kidney and liver function are among the signs and symptoms of EBOV disease, formerly known as hemorrhagic fever [1].

2. Risk factors and pathogenesis of Ebola

2.1. High-risk Factors

There are several risk factors that individuals have to take into consideration to help prevent the spread of this disease. One of the risk factors of Ebola is participation in traditional burial rituals as well as funeral practices such as washing well as touching Ebola-affected corpses. The other risk factor is percutaneous or being exposed to the blood or body fluids of persons infected by this condition. In addition, being a healthcare professional or aid worker providing care to infected patients increases the risk of one being infected by Ebola. This factor is a high risk, especially neglect of personal protective equipment [2].

2.2. Disease mechanism

The Ebola virus enters human body through mucosal surfaces, injuries, skin abrasions, or direct parental transmission. Once the virus enters the human body, it infects several types of cells, such as monocytes, macrophages, epithelial cells, dendritic cells, hepatocytes as well as adrenal cortical cells. Essentially, Ebola attacks all body cells except for lymphocytes. The Ebola virus enters these cells through various uptake mechanisms such as lipid rafts, micropinocytosis as well as receptor-mediated endocytosis [3]. The incubation period for this condition is 3 to 21 days, which often depends on the infection route [4]. After individuals have been infected by this condition, a rapid vital multiplication takes place, which is linked with an ineffective immunologic response. In essence, the virus moves from the site of infection to the regional lymph nodes before proceeding to the liver, spleen, and adrenal glands. This viral multiplication results in the exhibition of symptoms such as fever, headaches, myalgia, diarrhea, vomiting, abdominal discomfort as well as dehydration in infected persons [5]. As the disease advances to the final stages, it results in the decline of kidney and liver function, which can result in death as a result of mucosal bleeding and multiple organ failure within 16 days after the symptoms start to appear. Therefore, affected individuals need to seek medical care as soon as possible to help reduce the mortality rate of this condition [3].

During the early stages of Ebola infection, the soluble, non-structural secretory glycoprotein is produced in large amounts. This secretory glycoprotein combines with the neutrophil CD16b, which prevents the activation of neutrophils and causes lymphopenia, a key characteristic of Ebola infection. Although the human body produces IFN-α and IFN-β to prevent infection, the Ebola virus impacts the peripheral blood mononuclear cells, which prevent the production of type I IFNs and hinders the production of IFN-β. The inhibition of type I IFNs, which are responsible for inducing an antiviral state in the cells that have been infected by the Ebola virus and oversee the transition between innate and adaptive immunity, allows rapid viral replication to take place. The Ebola virus VP35 inhibits the production of IFN-β through multiple inhibitory effects, such as the disruption of the RIG-1 pathway as well as preventing IFN-inducible dsRNA and the Dicerdependent protein kinase R from activating. In addition, this condition causes a massive secretion of cytokines, chemokines as well as growth factors which induce numerous inflammatory mediators [3]. These cytokines are key drivers for the dissemination of Ebola because they play a vital role in recruiting myeloid cells, which are the supposed targets of this virus, to the inflammation sites. Essentially, these elevated numbers of inflammatory mediators result in a deregulated inflammatory immune response which is fatal because it is responsible for organ failure and sepsis syndrome. However, in cases where the human body can activate its innate immune response to control the inflammation, the infected person can survive an Ebola infection [6].

The Ebola virus also targets dendritic cells responsible for mediating innate and adaptive immunity. These cells are targeted because they are antigen-presenting and support the Ebola virus replication. Additionally, these cells are targeted because of their role in spreading the virus from their initial points of entry to the draining lymph nodes. In essence, the VP24, as well as the VP35 proteins of the Ebola virus, influence the normal expression of cytokines and chemokines, which impairs the differentiation of dendritic cells. Essentially, this impairment blocks the maturation of dendritic cells, which prevents the activation of lymphocytes, negatively impacting the human body's ability to produce immune cells s, which are responsible for mounting an antiviral response [6].

3. Social impacts of Ebola incidence

As established so far, Ebola has a fairly high mortality rate, and as a result, people tend to panic as soon as they learn of an outbreak. After the 2019 Ebola outbreak in the Democratic Republic of Congo, the incident revealed a lot of information about the social impacts of Ebola on the public. The hardest-hit social element in the then-Ebola hotspot was insecurity. The incidents of insecurity and violence witnessed in Congo at the time were a result of fears from locals of running out of food supplies in times of quarantine as well as scrambling for vaccines. The unrest was an additional

burden to the outbreak, and it increased transmissibility. The need for rapid response in the case of a confirmed Ebola Virus disease incidence to mitigate the health risk threat posed by the pathogens that cause the disease. The case DRC outbreak gave researchers, health workers, and scientists insight into the disease's transmission and allowed them a chance to learn from the experience how to best similar control outbreaks in the future. The insecurity and violence witnessed in DRC in 2019 following an outbreak in Kivu and Ituri posed a challenge to response efforts aimed at intervening to take control of the situation. At the time of the outbreak, there was the advantage of having an FDA-approved experimental vaccine which complemented intervention efforts. However, multiple armed groups, the extremely impoverished condition of the country, government distrust and displaced individuals counteracted the efforts aimed at fighting the outbreak of the Ebola virus disease. The attacks seem to have been coordinated by community resistance. The situation prompted respondents to adopt a new approach to help control the social elements of the outbreak, which saw a decline in new infections. Before the control phase, respondents were repeatedly attacked, which thwarted their efforts to stump the disease, a situation which resulted in a surge in new infections. The main takeaway from this incident is that a shift in approach to adapt to a difficult context on the part of respondents can significantly reduce the number of new infections, which results in a rapid fall in the number of new infections [7].

4. Prevention of Ebola

Although Ebola is a highly contagious infection, there are several measures that individuals can use to prevent this condition. The transmission of Ebola in humans takes place as a result of blood or bodily fluid contact between an infected person or animal [2]. Therefore, to prevent infection due to human-to-human transmission, one should avoid coming into contact with the blood and bodily fluids of infected persons. The contact can be avoided through the use of appropriate personal protective equipment and keeping away from items such as clothes, bedding, needles, as well as medical equipment that have come into contact with infected persons. In addition, individuals should avoid engaging in sexual activities with affected persons for twelve months or until the semen of Ebola male survivors' tests negative twice. Moreover, outbreak containment measures can be used to prevent this condition by ensuring a safe burial of affected persons, separating oneself from the sick to avoid transmission, and maintaining good hygiene practices. On the other hand, animal-to-human transmission can be prevented by thoroughly cooking animal products before intake and handling infected animals with protective clothing.

5. Treatment for Ebola

Several vaccines and pharmacological therapies have been approved as an intervention for Ebola. Dhama et al. state that the management of patients suffering from Ebola include quarantine, symptomatic, and supportive treatments. Supportive treatments are used to minimize mortality rates by increasing the chances of survival. Healthcare professionals provide supportive care through the provision of fluids as well as electrolytes and managing pain, infections as well as blood pressure that occur as a result of this condition. Furthermore, anti-diarrheal and anti-emetic medication interventions should be administered to patients to help manage the huge fluid loss. And also state that emergency therapeutics, such as passive immunization, consisting of neutralization antibodies through the transfer of sera from recovering to transmitted people, can be used as an intervention for this condition. This therapeutic approach is referred to as convalescence blood or serum transfusion, which aims to introduce antibodies from a recovered person to an infected individual to help neutralize or kill the virus [4].

Although supportive therapies are widely accepted, pharmacological interventions such as the use of Favipiravir can be used to treat Ebola. Favipiravir, which is used to treat influenza, has been found to be an effective intervention for Ebola [4]. The replication of this virus can also be stopped through

the use of Silvestrol, obtained from Aglaia foveolata. Host targeting agents can be used as an intervention for Ebola. Essentially, host targeting agents block the ebola virus through their interaction with host cell components. And using AMPK compound C, pyridinyl imidazole inhibitors, Geldanamycin, and epigallocatechin gallate to target essential host factors that are responsible for the entry of the Ebola virus into the human body. Moreover, herbal and natural products such as Prunella vulgaris, a Chinese herb, can be used for treatment because of its ability to inhibit the entry of the Ebola virus into the cells. Although this drug has been found to be effective, only two treatments have been approved by the United States Food and Drug Administration: Inmazeb and Ebanga. Ebanga has one monoclonal antibody, while Inmazeb has three used to stop the Ebola virus from replicating. Therefore, the most appropriate medical intervention should be Inmazeb and Ebanga since they are approved by the FDA, and the provision of supportive care to help ensure improved patient outcomes [8].

All in all, Ebola is a condition that is characterized by a high mortality rate and is caused by five different types of Ebola viruses. This condition is transmitted through blood or fluid contact with infected animals or persons, which makes it highly contiguous. Therefore, it is important for individuals to implement preventive measures such as the use of personal protective equipment to prevent the transmission of this condition. The Ebola virus targets dendritic cells because of their dissemination ability and causes a massive secretion of cytokines resulting in a deregulated inflammatory immune response that causes organ failure or death. However, supportive care or pharmacological interventions such as Inmazeb and Ebanga can be used to manage this condition. Therefore, it is important for infected persons to seek medical care to prevent Ebola from progressing to its fatal stages to help reduce the overall mortality rate of this condition.

6. FDA-Approved monoclonal antibodies for use against Ebola virus disease

Following the severe Ebola Virus disease between 2013 and 2016 in West Africa, America and other nations from around the world were prompted to accelerate the development of countermeasures against the disease. In the outbreak that followed, new investigational products were launched, and REGN-EB3 and mAb114 showed efficacy against the pathogen. After clinical trials, it was found that the products showed remarkably few side effects, which prompted the FDA to approve both REGN-EB3 and mAb114, a phenomenon which marked a monumental milestone in Ebola Virus Disease therapy. The fact that the two medication products can be produced in a relatively inexpensive production process made them suitable for application in the unique situation. From the incidence, scientific research, and clinical trials that took place, it is evident that the use of "mAbs in EVD patients appears to be safe and effective" even though there remain some knowledge gaps. For example, little is known concerning whether patients who get exposed to mAbs develop a robust immune response to future Ebola virus disease exposure. The challenge with the pathogens associated with the disease has fairly efficient mutation capabilities, which allow them to develop resistance to mAb therapy. Keeping the fact that a single mAb therapy may prove ineffective over time due to viral mutations, it is necessary to explore avenues for dealing with the problem of resistance [9].

As established so far, the American Food and Drug Administration (FDA) have approved REGN-EB3 and mAb114 as medicinal products for Ebola Virus therapy. However, someone feels that the focus should shift towards the development of easy-to-produce and economic therapeutics to help deal with exposure to the Ebola virus disease. The creation of a high-efficacy remedy to the virus starts with analyzing and understanding facets that make up the Ebola Virus disease, including its pathogenesis, epidemiology, diagnosis, treatment, and identifying therapy candidates as well as vaccine candidates, among others [10]. Most studies and remedies have been based on the virus's molecular mechanisms and the development of responses that interrupt or inhibit such mechanisms stopping further viral activity in the body. Such mechanisms include viral entry, replication processes, and immune system evasion techniques. Progress has been made following this line of research and clinical inquiry. Various studies and the contribution such studies have made in the specific area of

scientific and clinical research. For example, researchers have found three human single-chain antibodies (HuscFvs are HuscFv4, HuscFv11, and HuscFv14), in which case HuscFv4 efficacy neutralizes cell entry of particles with the same traits as the Ebola virus particles making the antibody a suitable therapeutic agency for infection. Ebola outbreaks are common in developing countries. As a result, there is a need to create a remedy that can be easily produced and stockpiled for emergency responses to deter the spread of the Ebola virus disease in case of an outbreak. Research studies are also necessary to create a permanent vaccine against the virus [10].

Vaccines are essential for controlling infectious diseases, especially in vulnerable populations. It is necessary to develop more medicines that are inexpensive, simple to store, and beneficial for low- and middle-income nations. The FDA authorized the rVSV-G-ZEBOV-GP vaccine (ERVEBO) on December 19, 2019, to protect anyone who is 18 years of age and older from contracting EBOV (Alizadeh et al., 2022). Utilizing immunoinformatic methods, the study's goal was to develop a multi-epitope vaccine against EBOV. The vaccine was non-allergenic and had all the desirable characteristics of a vaccination candidate, including good physicochemical properties, solubility, and high antigenicity. Molecular docking analysis and MD modelling were used to confirm the vaccine's high affinity for TLR4 and its stability, respectively [1]. The positive CAI value and high GC content from the codon optimization demonstrated the vaccine's expression in a bacterial host. The findings of this study were more spectacular due to the logical design of the linear structure of the multi-epitope vaccine, which was produced by the right arrangement of the chosen epitopes and adjuvant.

7. Mathematical study and drug modeling

A combination of three human monoclonal antibodies known as REGN-EB3 (Inmazeb) has been licensed for the treatment of Ebola infection. In a study, they developed a mathematical model to predict human survival using translational scaling and Ebola virus suppression by REGN-EB3 in a non-human primate (NHP) model. Data on pharmacokinetics and pharmacodynamics were included from single- and multiple-dose REGN-EB3 experiments infecting rhesus macaques. The antiviral mechanism of action was used as a forcing function in discrete indirect response models to cause the progression of key Ebola disease hallmarks, such as liver and kidney damage (elevated alanine [ALT] and aspartate aminotransferases [AST], blood urea nitrogen [BUN], and creatinine), as well as haemorrhage (decreased platelet count) To define the severity of the condition, a composite disease characteristic function was developed and merged with standard differential equations that predict the evolution of clinical biomarkers across time. The findings of the model simulation accurately depicted the concentration-dependence of the scope and progression of the pathophysiological and viral aspects of the Ebola infection, including the progression of viral load, ALT and AST increases, platelet count, creatinine, and BUN. The REGN-EB3 dose needed for saturation of the pharmacodynamic effects of viral suppression, reversal of Ebola pathophysiology, and survival were determined using the observed survival rate in rhesus macaques [11].

The model accurately scaled to people and predicted survival in clinical trials as well. This mathematical study reveals that drug-disease modelling might be a crucial translational tool to combine preclinical data from an NHP model that recapitulates the illness.

8. Conclusions

Ebola is a highly infectious viral disease which is usually spread through contact with the bodily fluids of an individual who is infected with the pathogen. Most fatalities result from the stage of Ebola virus infection when the immune system fails to give a robust response to exposure to the pathogens that cause the disease. Studies have led to an understanding of some atomic mechanisms of the Ebola pathogen, and the derived data has been used to inform therapeutic intervention. Understanding how the virus replicates after entering human cells is essential in the formulation of remedies, most of

which inhibit the pathogen's atomic activities. Through clinical trials, the FDA has approved two products for therapeutic interventions for Ebola patients.

However, there is still some room for improvement as some knowledge gaps, especially ones to do with drug resistance, remain a challenge to be met. This paper provides foundational information upon which further research concerning Ebola can be built.

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