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Treatment of Ebola Virus Disease

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In March 2014, the largest Ebola outbreak in history exploded across West Africa. As of November 14, 2014, the World Health Organization has reported a total of 21,296 Ebola virus disease (EVD) cases, including 13,427 laboratory-confirmed EVD cases reported from the three most affected countries (Guinea, Liberia, and Sierra Leone). As the outbreak of EVD has spread, clinical disease severity and national EVD case-fatality rates have remained high (21.2–60.8%). Prior to 2013, several EVD outbreaks were controlled by using routine public health interventions; however, the widespread nature of the current EVD outbreak as well as cultural practices in the affected countries have challenged even the most active case identification efforts. In addition, although treatment centers provide supportive care, no effective therapeutic agents are available for EVD-endemic countries. The ongoing EVD outbreak has stimulated investigation of several different therapeutic strategies that target specific viral structures and mechanisms of Ebola viruses. Six to eight putative pharmacotherapies or immunologically based treatments have demonstrated promising results in animal studies. In addition, agents composed of small interfering RNAs targeting specific proteins of Ebola viruses, traditional hyperimmune globulin isolated from Ebola animal models, monoclonal antibodies, and morpholino oligomers (small molecules used to block viral gene expression). A number of EVD therapeutic agents are now entering accelerated human trials in EVD-endemic countries. The goal of therapeutic agent development includes postexposure prevention and EVD cure. As knowledge of Ebola virus virology and pathogenesis grows, it is likely that new therapeutic tools will be developed. Deployment of novel Ebola therapies will require unprecedented cooperation as well as investment to ensure that therapeutic tools become available to populations at greatest risk for EVD and its complications. In this article, we review several agents and strategies that are now under active development.

Key Words: ebola, filovirus, hemorrhagic fever, immunization, infection, postexposure prophylaxis, therapy, treatment, vaccine, virus, viral diseases.

Overview of the Ebola Virus Disease Outbreak in West Africa

Filoviruses (family Filiviridae) are enveloped, negative-sense single-stranded RNA viruses that can reach lengths of 800–1400 nm. The virus family Filiviridae includes three genera: Cuvavirus, Marburgvirus, and Ebolavirus. Ebolavirus can be subdivided into the Zaire, Sudan, Tai Forest, Bundibugyo, and Reston Ebolavirus species. Since 1977, Ebola virus (EBOV) has been identified as a cause of severe disease in humans. Although the Bundibugyo, Zaire, and Sudan ebolaviruses have been associated with large outbreaks in Africa, the virus causing the 2014-15 West African outbreak belongs to the Zaire species.

Over the course of several outbreaks, clinical manifestations of disease have varied depending on the infecting species and other factors. Despite some variation, EBOV displays a uniform ability to cause systemic disease resulting...
from widespread viral replication and dissemination in a variety of organs. Ebola virus disease (EVD) progresses rapidly following initial infection and starts with an acute febrile illness and high-level viral replication, followed by severe immune suppression, sepsis, organ failure, and death. In the ongoing EVD outbreak, an analysis of patient outcomes in Sierra Leone showed a case-fatality rate of 74%. A meta-analysis of 20 EVD outbreaks, including the current outbreak, focused in West Africa using World Health Organization (WHO) data showed an estimated case-fatality rate of 65.4% (54.6–75.5%). Case-fatality rates have varied by EBOV species, age of infected individuals, country, and point in time when the outbreak was observed.

In the United States, EBOV gained public notoriety following the highly publicized isolation of a new EBOV species (Reston species) from imported cynomolgus monkeys in November 1989. Since then, several outbreaks have occurred across Africa, including Uganda, Democratic Republic of the Congo, Sudan, and Gabon, involving dozens to hundreds of cases. Together these outbreaks highlight the dramatic clinical presentation of EBOV infection and high case-fatality rates (near 90% in some outbreaks), and related research has shed further light on the striking morphology of the virus and distinct pathogenesis. Progress in understanding the origins of pathophysiologic changes that make EBOV infections of humans so devastating has been slow, in part because these viruses require special containment for safe research. However, an increasing understanding of the mechanisms of EBOV pathogenesis, facilitated by the development of new tools to elucidate critical regulatory elements in the viral life cycle, is providing new targets that can be exploited for therapeutic interventions.

In December 2013, EVD cases and deaths appeared in Guinea and represented the first reported cases in the present ongoing epidemic in West Africa (Figure 1). As of November 14, 2014, the World Health Organization (WHO) has reported a total of 21,296 EVD cases in Guinea, Liberia, and Sierra Leone, including 13,427 laboratory-confirmed cases; overall, the case-fatality rate based on total reported cases is 39.6% (8429 deaths). Although the greatest number of cases has been reported from Sierra Leone (10,124), reported deaths in Sierra Leone (case-fatality rate 30.2%) has been the lowest among the three most affected West African countries (Table 1). The magnitude of the present epidemic also marks it as the one with the highest number of survivors.

Clinical Course of Ebola Virus–Associated Disease

As a result of widespread dissemination of EBOV, a wide number of organs and tissues are directly infected with EBOV (Table 2). As a result, patients with EVD may show a broad range of clinical signs and symptoms. Clinically, EVD manifestations may include high fever, headache, malaise, fatigue, nausea, vomiting, diarrhea, hypotension, and bleeding. Disease due to EBOV has been associated with a relatively high case-fatality rate ranging from 40% to 90%, and in outbreaks prior to 2014, treatment had been largely limited to supportive care, including antipyretics and rehydration. Major clinical disease due to EBOV is associated with gastrointestinal tract dysfunction, including electrolyte abnormalities (diarrhea, vomiting, hypokalemia, hyponatremia, and hypocalcemia). Because of rapid disease progression, patients with EBOV infection require early and aggressive therapeutic management with supportive care that includes oral or intravenous rehydration, and intensive care. In some cases, patients may progress to develop sepsis or respiratory failure requiring mechanical ventilation. Gastrointestinal tract fluid losses may be significant and lead to hypovolemic shock and organ failure. If available, careful clinical management and monitoring of fluid loss as well as hypotension are essential to reduce the risk of renal failure and cardiovascular collapse.

Ebola Virus Pathogenesis

Previous studies have shown that inoculation with EBOV is rapidly followed by viremia, with the virus spread throughout the host’s tissue and organ systems. Animal studies suggest that EBOV viremia starts from 2 to 4 days after inoculation. An early target of the EBOV appears to be cells of the mononuclear phagocyte system—especially macrophages. As a result, EBOV replication in the lymph nodes and spleen occurs early in the disease course. Later stages of infection are characterized by EBOV replication in the interstitial fibroblasts of various tissues, including the lungs. More recent studies in the macaque animal model showed that dendritic cells are early and sustained targets for EBOV, and this target, in part, explains the
immunosuppression induced by EBOV. In animal studies and human disease, disseminated intravascular coagulation has been observed. In addition, animal studies have shown that the EBOV transmembrane glycoprotein GP(1,2) and the EBOV matrix protein VP40 activate endothelial cells and induce a decrease in barrier function. This viral effect likely contributes to hypotension and vascular instability. This decreased endothelial cell function appears to be compounded by activation of cytokine tumor necrosis factor-α, which is known to induce a long-lasting decrease in endothelial cell barrier function and is hypothesized to play a key role in EBOV pathogenesis.

Immunologic System Dysfunction and Dysregulation in Ebola Virus Disease

EBOV exerts many of its early and lasting effects through immune dysregulation. Accumulating evidence indicates that the virus actively subverts both innate and adaptive immune responses and triggers harmful inflammatory responses as the virus inflicts direct tissue damage. The host immune system is ultimately overwhelmed by a combination of inflammatory factors and virus-induced cell damage, particularly in the liver and vasculature, often leading to death from septic shock. EBOV is very effective in inducing host immunosuppression through two of its eight viral proteins. These include the viral protein (VP) 35, and VP24. VP35 binds double-stranded RNA and antagonizes several antiviral signaling pathways. VP24 binds transporter molecules to prevent STAT1 translocation and, more recently, studies suggest that VP24 also binds STAT1 directly. In this way, VP24 appears to interact in two distinct interferon pathways. Differences in the structures of VP35 and VP24 among different EBOV strains may provide clues to
Explain differences in the pathogenesis among the EBOV strains.

Therapeutic and Prophylactic Strategies for Ebola Virus Disease

Treatment of EVD can be considered in the context of treatment and prophylaxis windows of opportunity (Figure 2). In the absence of pre-exposure prophylaxis (disease prevention) through use of nonpharmacologic means (e.g., barrier precautions) or vaccines, the availability of antiviral agents would offer opportunities for postexposure prophylaxis (secondary prevention) as well as postexposure treatment to reduce disease severity, virus transmission, and duration of clinical manifestations, and to achieve disease cure. In situations where postexposure prophylaxis is considered, health care providers would ideally administer the intervention as soon as credible risk of exposure to a symptomatic patient with EVD is confirmed. Depending on the clinical presentation and disease progression, therapeutic agents would ideally be available in different formulations that permit oral, intramuscular, or intravenous administration. In the context of the ongoing outbreak, should an effective and approved postexposure prophylactic agent become available, a number of practical issues warrant consideration, including the following: frequency and duration of prophylaxis, pediatric dosing, renal failure dosage adjustment, geriatric dosage adjustment, and indications for discontinuation of prophylaxis; measurement of end-organ function and immune system function, and vital signs (e.g., body temperature, blood pressure) to monitor for drug-related adverse events as well as disease progression; and drug supply availability, and cost. To address these issues, pediatric, adult (particularly older adults), and special patient treatment guidelines will be needed as soon as possible.

Historically, therapeutic agents against hemorrhagic fever viruses have been of interest for decades. In the late 1970s and into the 1980s, interest in antivirals also grew with reporting of Lassa fever outbreaks. In one of the earlier reports for Lassa fever, Jahrling and colleagues evaluated the effect of ribavirin in rhesus mon-
keys, and these early results suggested that ribavirin may be effective for humans with Lassa fever. In a later study reported in 1982, Canonicco and colleagues showed that pyrazofurin could inhibit in vitro viral plaque formation but did not confer protection in the mouse model. Then, in 1986, McCormick et al. reported the effectiveness of ribavirin therapy for patients with Lassa fever in Sierra Leone. Additional studies also suggest that ribavirin may be effective against Junin and Machupo virus infections causing Argentine and Bolivian hemorrhagic fever, respectively. Early trials of ribavirin therapy, however, showed that it was not effective against filoviral-associated disease, including EVD.

Current Status of Antiviral Compound Development for Treatment of Ebola Virus Disease

For several years, research on EBOV and development of novel therapeutics and vaccines has been challenging, in part because the virus must be handled in biosafety level 4 facilities. Work on biosafety level 4 agents requires that researchers conduct studies in high containment laboratories that are available in a relatively limited number of facilities worldwide. In the past several years, a number of laboratories and industry-based researchers have used reverse genetics to identify new targets within viral genomes for drug and vaccine development. Reverse genetics allows development of recombinant filoviruses, such as EBOV, that contain key gene sequences but are nonreplicating and therefore noninfective. Reverse genetics has been applied in EBOV research to understand gene function as demonstrated in a study by Martinez and colleagues. This team conducted studies of the EBOV VP30 and developed a model for VP30 phosphorylation that is dynamic and represents an important mechanism for regulation of the EBOV replication cycle. In another study by Blaney et al., reverse genetics was applied to express a Zaire EBOV (ZEBOV) glycoprotein. This team created a rabies virus (RABV) vaccine that efficiently expresses ZEBOV glycoprotein and induces humoral immunity against both RABV and ZEBOV, while conferring protection against lethal RABV and EBOV challenge in mice. Reverse genetics has also enabled creation of virus-like particles (VLPs) that have morphology identical to actual EBOV but are nonpathogenic. These VLPs, generated in a plasmid-based system, allow study of EBOV entry, replication, and assembly without the need for biosafety level 4 containment. Such a system has potential application in the development of EBOV vaccines. Finally, reverse genetic techniques for EBOV have allowed high-throughput screening to identify potential drug targets on the virus without requiring biosafety level 4 containment facilities.

Nucleoside Analog Candidate Therapies

In 2014, antiviral research and development efforts have focused on identifying safe and efficacious agents that may be used as postexposure treatment (Table 3). One such agent, T-705 (favipiravir) has undergone animal trials to evaluate its efficacy against EBOV. Favipiravir is a pyrazinecarboxamide derivative and has been shown to be efficacious against ZEBOV in vitro and in vivo. Animal studies have confirmed that favipiravir is effective in treating animals infected with the aerosolized E718 strain of EBOV. More recently, studies suggest that favipiravir induces viral mutagenesis that leads to reduced viral infectivity and replication. The agent has broad antiviral effects and was originally developed as an agent against influenza viruses.

Brincidofovir (BCV) is a lipid conjugate of the acyclic nucleotide phosphonate cidofovir and was developed as an antiviral against double-stranded viruses. Although clinical trials to study BCV’s efficacy against human cytomegalovirus (CMV), smallpox, and adenovirus infections are ongoing, BCV has also been given Investigational New Drug status by the US FDA as a potential treatment for EBOV due to BCV’s demonstrated in vitro activity against EBOV (http://ir.chimerix.com/). An open-label, multicenter trial of BCV is now planned in humans to study safety and tolerability during treatment of EBOV infection (clinicaltrials.gov; ClinicalTrials.gov Identifier: NCT02271347).
<table>
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<th>Agent</th>
<th>Manufacturer</th>
<th>Stage of Evaluation</th>
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<td>JK-05</td>
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FDA = U.S. Food and Drug Administration.
In China, a novel antiviral compound, referred to as JK-05, has been approved for treatment of EBOV infections. This compound has reportedly been developed and tested by China’s Institute of Microbiology Epidemiology of the Academy of Military Medical Sciences. This compound appears to act on RNA viral polymerase to inhibit viral replication and has undergone preclinical testing in animal models. JK-05 has been approved for emergency use only, and no human trial data are available at this time. Plans for clinical trials or distribution of this therapy in West Africa have not been announced at this time.

Another viral nucleoside analog, BCX4430, has recently received substantial attention as a potential treatment for EBOV infections. BCX4430 is a novel adenosine analog that inhibits the viral RNA polymerase function by incorporating into new viral RNA chains and causing chain termination. When administered intramuscularly, BCX4430 has shown clinical protection in mouse and guinea pig models, even when administered after exposure. From a safety perspective, it is worth noting that BCX4430 did not incorporate into human RNA or DNA. Currently, the timing of treatment for drugs such as BCX4430 is not settled, although early treatment to high-risk or potentially exposed individuals may be an option. Administration of BCX4430 may be feasible through the oral route, although pharmacokinetics data suggest that the intramuscular route may provide more favorable therapeutic levels.

These results highlight the fact that secondary prevention or treatment following exposure may be optimized within a well-defined window period. Previous studies of experimental postexposure therapies, including convalescent serum immunoglobulin (Ig) G, monoclonal antibodies, and antiviral compounds, have examined survival following EBOV infection. Additional studies are needed to understand optimal dosing, routes of administration, and durations of therapy.

RNA-Silencing Molecules and Antisense Oligomers

RNA silencing (sometimes referred to as RNA interference [RNAi]) is a regulatory mechanism for gene expression that is associated with control of cell differentiation and development. RNAi also serves as an innate antiviral response in plants, nematodes, and insects. In mammals, viruses code for RNA silencing suppressors (RSSs) that enable viral replication at higher titers. A number of human viruses have been shown to encode RSSs, including EBOV. In fact, the EBOV VP35 protein is a suppressor of RNAi in mammals, and its RSS activity is functionally equivalent to that of the human immunodeficiency virus (HIV)-1 Tat Protein.

Prior to the current EVD outbreak, scientists in one trial identified small RNAi molecules (sometimes referred to as small interfering RNAs [siRNAs]) that were effective in protecting guinea pigs against lethal challenge with EBOV. SiRNA molecules are fragments of double-stranded RNA that inhibit viral messenger RNA (mRNA) and viral replication. In this trial, four siRNA molecules were created to target the polymerase (L) gene of ZEBOV. The siRNA molecules were complexed to polyethylenimine (PEI, a polymer composed of repeating amine units) or formulated in stable nucleic acid lipid particles. Administration of the RNAi molecules with PEI or the nucleic acid lipid particles with PEI or the nucleic acid lipid particles provided greater protection against viremia and death in a guinea pig model when administered shortly after EBOV challenge. In a further study of siRNA molecules administered in nonhuman primates, molecules targeting EBOV L polymerase, VP 24, and VP35 were administered in a postexposure trial. Results suggest that the RNAi therapy provided complete protection and was well tolerated.

In addition, studies are now initiated to evaluate lipid nanoparticle/siRNA referred to as TKM-Ebola. Phase I trials of TKM-Ebola were initiated (http://clinicaltrials.gov/show/NCT01518881). In March 2014, TKM-Ebola was given fast-track approval by the U.S. Food and Drug Administration. In addition, TKM-Ebola is now entering human clinical evaluation in Guinea for emergency use in treating patients with EBOV, in collaboration with a consortium led by the WHO. The TKM-Ebola molecule undergoing evaluation has been designed to target the Guinea variant of the ZEBOV species.

An additional active area of research focused around development of small molecule therapeutics uses antisense phosphorodiamidate morpholino oligomers (PMOs) to target sequences of viral mRNAs corresponding to VP24, VP35, and the RNA polymerase L protected rodents in both preexposure and postexposure therapeutic regimens. Two specific PMOs (AVI-6002 and AVI-6003) have undergone phase I trials. AVI-6002 was evaluated for postexposure treat-
ment of EBOV infection, and AVI-6003 was studied for Marburg virus infections. AVI-6002 is composed of two PMOs referred to as AVI-7537 and AVI-7539, whereas AVI-6003 is composed of AVI-7287 and AVI-7288. In two separate phase I safety and dose-escalation studies, 30 healthy male and female subjects between 18 and 50 years of age were enrolled in six cohorts of five participants each. Each volunteer received a single intravenous infusion of active drug (AVI-6002 or AVI-6003) or placebo, with the dose escalated in each subsequent cohort. AVI-6002 was found to be well tolerated.

Immunotherapeutics

The use of passive immune therapy or convalescent immune plasma for treatment of EVD dates back to earlier epidemics, such as the 1995 outbreak in Kikwit, Zaire. Mupapa and colleagues treated eight patients who met the case definition for EVD with passive immune therapy; of those patients, seven survived. In 2007, Jahrling and colleagues reported additional data from nonhuman primates treated with whole blood from EBOV-challenged nonhuman primate survivors. Results of this nonhuman primate trial demonstrated no beneficial effect following the administration of convalescent-phase blood shortly after EBOV challenge. In the 2014–15 epidemic, a limited number of patients with EVD have undergone treatment with convalescent IgG that was administered along with supportive care and EBOV-specific antivirals and monoclonal antibodies. Although no controlled trials of anti-EBOV IgG have been performed, additional challenges remain in obtaining EBOV convalescent IgG in populations where there may high background rates of HIV, hepatitis B, or hepatitis C infection. To address the potential use of blood products from EVD survivors, the WHO has issued recent guidelines for use of convalescent whole blood or plasma as empiric treatment during outbreaks. Several important topics are covered in these guidelines, including the identification of suitable blood and/or plasma donors among EVD survivors, donor consent and selection, donor blood collection, and donor care, as well as storage of whole blood and plasma, inventory management, and transportation. Other guidance includes advice on transfusion of convalescent whole blood and plasma, with key topics, including selection of patients with EVD, informed consent, collection of patient’s blood samples for laboratory testing, selection of convalescent whole blood or plasma unit for transfusion, administration of whole blood or plasma, and patient monitoring. Those sites considering the use of convalescent whole blood and/or plasma can use these guidelines to better understand if their facility has sufficient resources to administer such products.

In 1999, two studies were reported that administered hyperimmune globulin in animal models. Mixed results were reported in guinea pig, mouse, and cynomolgus monkey models. In guinea pigs, hyperimmune globulin treatment was effective if administered at the time of EBOV challenge. However, no beneficial effects were observed in either the mouse- or monkey-challenge models. Evidence presented in this report suggests a beneficial effect in guinea pig, baboons, and humans. Human administration of anti-EBOV hyperimmune globulin in this study was conducted for laboratory researchers who were accidentally exposed to EBOV.

A novel immunotherapeutic, consisting of a combination of monoclonal antibodies (mAb), has undergone success in animal studies and is now undergoing further evaluation following its administration to approximately seven patients with EVD in the United States and other countries. Recently, the composition of the mAb combination (now referred to as ZMapp) was described. The results of this study suggest that individually, the mAbs bind the EBOV glycoprotein core. ZMapp is currently manufactured in a tobacco plant–based production facility where plants are genetically modified to express monoclonal antibodies to EBOV glycoproteins. The present formulation of ZMapp is a combination of two mAb cocktails referred to as Mb-003 and ZMab. Currently, ZMapp is in short supply, but plans are under way to scale up production to meet potential demand in the current West Africa EVD outbreak.

Conclusion

The ongoing outbreak of EVD in West Africa has led to a record number of cases and deaths.
Control of this current EVD outbreak and future epidemics is likely to require a multifactorial strategy that includes high-quality disease surveillance, rapid diagnosis, and access to safe and effective therapies. Among the current group of potential therapies for EVD, it is hoped that safe and effective agents will emerge from a diverse group under evaluation that now includes nucleoside analogs, RNA silencers (siRNAs), and a range of immunotherapeutics, including convalescent whole blood or plasma, and targeted monoclonal antibodies. The international community, including a consortia of public and private organizations, with leadership from the WHO and national governments, is now mobilized to accelerate research and development of existing and new therapeutic agents for the treatment of EBOV. Within such collaborations, diverse expertise from pharmacists, clinical trialists, public health officers, educational specialists, community health workers, epidemiologists, physicists (including generalists and specialists), anthropologists, sociobehavioralists, psychologists, and economists will be needed. Additional expertise in pharmacokinetics, pharmacodynamics, and pharmacogenomics will be crucial in accelerating the development and deployment of effective treatment regimens. Fortunately, a diverse pipeline of agents is now under evaluation in both animal and human trials, with evaluations now under way or planned in EBOV-endemic regions. In the next several months, additional agents and combination therapies are likely to be reported and identified. Aggressive global development of novel EVD therapies will require unprecedented cooperation as well as investment to ensure that therapeutic tools are available to populations at greatest risk for EVD as well as complications and death due to EVD. Such therapeutic tools will also be needed for treatment of health care workers on the front lines in caring for patients with EVD in the affected countries of Africa and other regions.

References


