Potential clinical treatment for Ebola pandemic

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West African countries are currently suffering the most severe pandemic of Ebola virus disease ever recorded, with 4269 human cases and 2288 deaths (through 6 September 2014), and the number of cases in the current outbreak exceeds the number from all previous outbreaks combined. Ebola virus disease was first described in 1976 originating from the Ebola River in the Democratic Republic of the Congo. Five Ebola viruses have been reported to cause Ebola virus pandemics, including Zaire Ebola virus, Sudan Ebola virus, Ivory Coast Ebola virus, Reston Ebola virus and Bundibugyo Ebola virus. The Zaire Ebola virus is the most deadly with a fatality rate up to 90%. Unfortunately, the current outbreak in the West African countries is caused by the Zaire Ebola virus, and no specific treatment for the disease is yet available.

Like other filoviruses, Ebola virus has the special thread-like structure seen on electronic micrographs. Ebola virion contains a linear, single-stranded negative-sense RNA genome, which is approximately 19,000 nucleotides in length without a polyadenylated 3′ terminus or a 5′ capped end. The genome encodes seven structural proteins and one non-structural protein ordered 3′–leader–nucleoprotein (NP)–viral protein VP35–VP40–glycoprotein (GP)/secreted GP (sGP)–VP30–VP24–RNA-dependent RNA polymerase (L)–trailer–5′. The leader and trailer are non-transcribed regions but are important signals that control the transcription, replication and packaging of the viral genomes into new virions. Glycoprotein (GP) is the main viral determinant of Ebola virus pathogenicity.

The outbreaks of Ebola virus disease have been primarily restricted to Africa. This restriction may be because Ebola virus disease kills infectors at a high mortality rate and governments and individuals always respond quickly to quarantine these areas. The natural reservoir(s) and primary transmission route(s) of Ebola virus disease are not entirely clear. It is reported that bats could be a possible reservoir, and they may support the replication of Ebola virus without symptoms of the disease. Ebola virus disease is believed to occur after an Ebola virus is transmitted to a human via contact with an infected animal. Human-to-human transmission appears to occur through direct contact with blood or other body fluids from infected patients or by contact with contaminated medical equipment, so barrier nursing is necessary to limit the spread of infection. A report from Natural News confirmed that Ebola can be transmitted through aerosols and that the virus can survive for days outside a host (http://www.naturalnews.com).

The incubation period of Ebola virus ranges from 2 to 21 days (http://www.cdc.gov/vhf/ebola/symptoms/index.html).

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The abrupt onset of Ebola hemorrhagic fever resembles the common flu with clinical symptoms, such as fever, headache, sore throat, weakness, myalgia, abdominal pain, diarrhea, and vomiting. Haemorrhagic manifestations arise during the peak of the illness. The liver, kidney, and spleen are damaged by the Ebola virus, leading to serious bleeding and coagulation abnormalities, including gastrointestinal bleeding and a range of hematological irregularities, such as lymphopenia and neutrophilia. When the virus attacks reticuloendothelial cells, cytokines are over produced and cause an exaggerated inflammatory response that is not protective. The microvascular endothelial cells are eventually infected by the Ebola virus, and the vascular integrity is destroyed. The terminal stages of Ebola virus infection usually include diffuse bleeding, and hypotensive shock accounts for many Ebola virus fatalities.

Until now, we have had no effective vaccines or treatments for Ebola virus. Therefore, comprehensive treatment including supportive therapy is most important, such as balancing fluids and electrolytes, maintaining oxygen levels, and injecting anticoagulants. However, several prospective treatment methods are being studied. rNAPc2, nematode-derived anticoagulation protein, has shown 33% efficacy in the treatment of macaque infected with Zaire Ebola virus. It plays an important role in weakening coagulation and inflammatory [1]. T-750 (favipiravir) is a pyrazinecarboxamide derivative and inhibits influenza virus replication. T-750 is being tested in the late clinical stage, and it seems to effectively treat Ebola virus disease in a mouse model. Favipiravir can be converted to T-705-ribofuranosyl-50-triphosphate, a nucleotide analog that can inhibit the viral RNA-dependent RNA polymerase or induce lethal mutagenesis by incorporating into the viral RNA [2]. BCX-4430, a new nucleotide analogues, inhibits virus replication by inhibiting viral RNA polymerase function. It exhibits broad-spectrum antiviral activity against numerous viruses, including flaviviruses, bunyaviruses, and coronaviruses [3]. The serum of recovered patients may also be useful to develop a treatment for Ebola virus disease. During this outbreak of Ebola virus in the West African countries, two Americans became infected, and they benefited from a cocktail antibody treatment, called ZMapp, which is a mixture of three humanized mouse monoclonal antibodies (c13C6, h-13F6, and c6D8). The three anti-Ebola virus monoclonal antibodies had significantly protected rhesus macaques from a lethal challenge of Ebola virus [4]; however, no human safety studies were performed before the drug was administered to these two patients. The FDA has approved ZMapp for the treatment of patients infected with Ebola virus in the current emergency situation. The antisense technology can also be used to treat Ebola virus disease. Warren et al. [5] reported that small interfering RNAs and phosphorodiamidate morpholino oligomers may effectively prevent Ebola virus disease in nonhuman primates by targeting the Zaire Ebola virus RNA polymerase L protein.

Based on this technology, TKM-Ebola has also been approved by the FDA to treat patients infected with Ebola virus. However, these experimental treatments have no recorded human safety trials. Some drugs approved for human use for other indications, including chloroquine [6], estrogen receptor (clomiphene and toremifene) [7], ion channel blocker (amiodarone, dronedarone and verapamil) [8] and imatinib [6], have shown activity against Ebola virus infection or entry *in vitro* or in rodent models. These drugs would be candidates for treating EHF, alone or in combination with other antiviral drugs.

The common, broad-spectrum, antiviral drug Ribavirin might only be effective among moderately ill patients, similar to Crimean-Congo hemorrhagic fever (CCHF). Ribavirin is a synthesized guanosine analog that may inhibit RNA-dependent RNA polymerase, mutagenize the genome and inhibit inosine monophosphate dehydrogenase (IMPDH), which is a key enzyme for *de novo* purine nucleotide biosynthesis [9]. In addition to anti-viral treatments, we could also consider medicines that provide vascular protection. Rutin, or vitamin P, is a major flavonoid that can be used in CCHF and epidemic hemorrhagic fever to protect vascular barrier integrity. Cell adhesion molecules (CAMs), including selectin, intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), play critical roles in cell adhesion to the vascular endothelium resulting in extravasation of cells and vascular inflammation. Rutin can inhibit the expression of CAMs, thus inhibiting the adhesion and migration of leukocytes and affecting vascular barrier integrity [10,11]. Vitamin C, or ascorbic acid, can also be used in CCHF and epidemic hemorrhagic fever [11]. It may prevent the endothelial dysfunction via stimulating endothelial proliferation, modulating blood flow by sparing endothelial cell-derived nitric oxide and increasing the level of type IV collagen in the basement membrane [12]. High-dose methylprednisolone also effectively treats patients with CCHF [13]. Activation of NF-κB could upregulate the proinflammatory cytokines followed by endothelial cell dysfunction. Research showed that blockade of NF-κB activation preserved endothelial barrier integrity. Patel et al. [14] reported that statins had the role of anti-inflammatory and immunomodulatory by downregulating expression levels of NF-κB, sCD40L and sICAM. In addition, it can also decrease expression of tissue factor and thrombin and increase activation of thrombomodulin [15]. Currently, statins have been used in the treatment of cardiovascular disease, which could be considered for treating patients with EHF.

Ebola virus disease is a painful reminder, all individuals who have been to the infected area should be isolated for at least two weeks. To prepare for the Ebola virus pandemic, besides detection materials, we should store enough drugs specific to Ebola virus disease and commonly used drugs for hemorrhagic fever.

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