Potential Treatments Against Ebola Virus Disease

Brincidofovir\textsuperscript{1-5}: Brincidofovir is a lipid antiviral conjugate of cidofovir, a nucleotide analogue with broad-spectrum in\textit{vitro} activity against herpesvirus, cytomegalovirus, varicella zoster virus, adenovirus, polyomavirus, poxyvirus, and papillomavirus. As these are as DNA viruses, it is unclear why when tested against the RNA Ebola virus that brincidofovir demonstrated antiviral activity. Brincidofovir has been studied in clinical trials in humans to prevent cytomegalovirus infection and as salvage therapy against severe adenovirus infection in immunocompromised hosts. Gastrointestinal intestinal side effects including diarrhea are the dose-limiting toxicity at approximately 200 mg by mouth twice weekly. As of 10/29/14, it has been publicized that 3 patients have received brincidofovir, 2 in combination with convalescent blood transfusions. The 2 combination therapy patients have survived. See the UWHC brincidofovir monograph for more details.

ZMapp\textsuperscript{6-8}: ZMapp is a combination of three mouse and human chimeric IgG1 monoclonal antibodies (c2G4, c4G7, and c13C6). ZMapp is specifically designed for the treatment of Ebola virus disease, but has never been studied in humans. ZMapp provides passive immunity by binding directly to viral proteins and activating the immune system to clear the virus. When given to Rhesus monkeys infected with the Ebola virus, even those nearing the clinical limit for euthanasia had a full recovery. The monkeys were given 50 mg/kg IV every 72 hours for 3 doses. As of 10/29/14 it has been publicized that 3 humans have received ZMapp as experimental therapy with 2 survivors. See the UWHC ZMapp monograph for more details.

TKM-Ebola\textsuperscript{9-13}: TKM-Ebola is a combination of small interfering RNA molecules that block enzymes catalyzing the replication of RNA. A trial of TKM-Ebola was halted due to the observation of cytokine release seen at higher doses. Due to the new circumstances surrounding the current epidemic, the FDA has modified their hold and may allow the company to make the drug available to infected individuals. TKM-Ebola is a combination of small, interfering RNA (siRNA) molecules that bind to RNA-dependent RNA polymerase L (EK-1), virion protein 24 (VP 24), and virion protein 35 (VP 35). These 3 molecules were then formulated as stable nucleic acid-lipid particles (SNALPs) in a novel lipid nanoparticle delivery technology. When 4 doses were given to non-human primates, 66.6% (2/3) were rescued from otherwise lethal doses of Ebola virus. When 7 doses were used, protection increased to 100% (4/4), with a noted moderate increased in serum aspartate aminotransferase. As of 10/29/14, it has been publicized that 1 patient has received TKM-Ebola in combination with convalescent blood transfusions. See the UWHC TKM-Ebola monograph for more details.

BCX4430\textsuperscript{14-16}: BCX4430 is about to begin Phase I testing for the experimental treatment of Ebola virus-infected patients. In macaque studies, BCX4430 was dosed at 15 mg/kg orally, intramuscularly, or intravenously twice a day. Against the Marburg virus, BCX4430 was able to rescue 5 out of 6 macaques when started 1 to 48 hours after inoculation with lethal amounts of virus. The drug was well tolerated with no observed adverse effects. In\textit{vitro} studies additionally show that BCX4430 works by inhibiting viral RNA polymerase. It has broad-spectrum antiviral activity, including against the Ebola virus. See the UWHC BCX4430 monograph for more details.
Convalescent serum from patients who have survived Ebola virus infection\textsuperscript{17}: There are no studies available on the use of convalescent serum to treat Ebola virus disease; however it has been used in the United States and West Africa. An unknown amount of patients in Africa have received this therapy. In the United States, 4 patients have received such treatment, 3 of them in combination with an additional experimental treatment. Currently the World Health Organization does recommend this approach, with the precaution that the numbers are too small to support any conclusions about efficacy. There is an interim guidance document from the WHO available online.

Selective estrogen receptor modulators (SERMs)\textsuperscript{18}: A cell-based screen of all FDA approved and ex-FDA approved drugs and molecular probes using enhanced green fluorescent protein and flow cytometry, fluorimetry, fluorescence microscopy, and high-content imaging was used to identify inhibitors of the Ebola virus. The SERMs clomiphene and toremifene were identified. Broad anti-filovirus activity, including anti-Ebola, was then confirmed \textit{in vitro} and in a murine model, even when the expression of estrogen receptors was knocked out. The mechanism of inhibition appears to involve cellular entry of the virus, and is dependent on the molecular structure being a class II cationic amphiphile. Current efforts are focused on the development of clomiphene and toremifene alone or synergistically with other agents in development. Non-human primate trials are needed.

Recombinant nematode anticoagulation protein (rNAPc2)\textsuperscript{19}: As the Ebola virus induces the expression of procoagulant tissue factor in primate monocytes and macrophages, an inhibitor of Factor VIIa/Tissue Factor was developed. rNAPc2 rescued 33\% of macaques in the rNAPc2 treatment groups after lethal inoculation of Ebola virus, and the treated macaques who did succumb to Ebola virus disease did so after 11.7 days instead of 8.3 (\(p = 0.0184\)). D dimer, fibrin deposits, intravascular thromboemboli, interleukin-6, and monocyte chemoattractant protein-1 (MCP-1) were all reduced in the treated groups. rNAPc2 was never studied in humans, but did lead to the development of recombinant human activated protein C (rhAPC).

Recombinant human activated protein C (rhAPC)\textsuperscript{20,21}: Advanced Ebola virus disease is thought to mimic severe sepsis, and a trial with rNAPc2 (above) showed some benefit in macaques, so a trial was performed to see if rhAPC may be beneficial. 14 macaques were given a lethal dose of Zaire Ebola virus, and 11 of them got rhAPC 30 minutes afterwards, continuing for 7 days. The 3 control macaques died on day 8. 2 of 11 rhAPC-treated macaques survived, and the other rhAPC-treated macaques died, but on mean day 12.6. The study concluded advanced, late Ebola virus disease and severe sepsis may share underlying mechanisms and therefore treatments as well. Xigris (drotrecogin alfa) was brought to market to improve outcomes in patients with severe sepsis, but was withdrawn in 2011 after no efficacy could be demonstrated.

Retinazone\textsuperscript{22}: Retinazone is a novel vitamin A-derived (retinoid) thiosemicarbazone derivative with \textit{in vitro} data first published in April 2014. The mechanism of action is covalent inactivation of iatrogenic and intraexonic viral glucocorticoid response elements. Retinazone is purported to be the first antiviral agent capable of eradicating HIV and HBV proviruses from their human host. Additionally, retinazone was tested \textit{in vitro} against the 1976 Zaire strain of Ebola virus with potent inhibition noted. There are no \textit{in vivo} trials.
Melatonin: According to an article in the Journal of Pineal Research, melatonin reportedly directly targets the all of the immuno-inflammatory responsive events associated with Ebola virus disease infection (suppression of TNF- α, IFN- α, IL6, IL8, TF, MCP-1, VEGF, phosphorylation of JNK, and the degradation of the tight junctional proteins and it reduces endothelial apoptosis. It serves as a free radical scavenger and an anti-inflammatory agent. Melatonin also has anticoagulant activity that has led to its use in disseminated intravascular coagulopathy. Melatonin is not an anti-viral, but it may retard the body’s excessive immune-inflammatory response to the Ebola virus. High doses >20 mg PO or IV are likely needed to see any effect. There is no data for use in patients with Ebola virus disease.

Ribavirin: Ribavirin has demonstrated no activity against the Ebola virus.

Favipiravir: Favipiravir is a substituted pyrazine compound currently being studied in phase III uncomplicated influenza trials in the United States. It has demonstrated protection of rodents from filoviruses and primate trials may be beginning soon.

References:


Author: Ron Kendall, PharmD PGY-2 ID

Date: 10/29/14