Administration of Brincidofovir and Convalescent Plasma in a Patient With Ebola Virus Disease

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From 2014 to May 2015, >26 000 Ebola virus disease (EVD) cases were reported from West Africa. We present a patient with EVD who received brincidofovir and convalescent plasma. The relative contributions of supportive care, investigational therapies, and patient’s immune-response on survival could not be determined. Randomized trials are needed.

Keywords. Ebola; investigational therapies; trials.

The 2014–2015 Ebola virus disease (EVD) epidemic due to Zaire ebolavirus (EBOV) is the largest EVD outbreak in history. As of 3 May 2015, a total of 26 628 confirmed, probable, and suspected cases of EVD with 11 020 deaths have been reported from 6 West African countries (Guinea, Liberia, Sierra Leone, Mali, Nigeria, and Senegal), Spain, the United Kingdom, and the United States [1]. Of these, 868 confirmed EVD cases and 507 deaths have been reported among healthcare personnel in Guinea, Liberia, and Sierra Leone [1]. No approved therapeutic agents for EVD are available, although several therapies have been in development (BCX-4430, TKM-Ebola, ZMapp, AVI-7537, favipiravir, and brincidofovir) [2, 3]. We present the first EVD case treated with the investigational drug brincidofovir and convalescent plasma. The manufacturer and the Food and Drug Administration (FDA) made brincidofovir available for compassionate use through an emergency Investigational New Drug (IND) application. Convalescent plasma was obtained from an EVD survivor and made available for compassionate use through a different emergency IND.

CASE REPORT

A 33-year-old previously healthy man was transferred from Monrovia, Liberia, to the Nebraska Biocontainment Unit in Omaha with a diagnosis of EVD. The patient presented to an Ebola treatment unit (ETU) in Monrovia with fever and myalgias, and tested positive for EVD by reverse transcription polymerase chain reaction (RT-PCR). Subsequently, he developed generalized weakness, nausea, and watery nonbloody diarrhea that slowly increased in frequency. At the Monrovia ETU he received hydration, metoclopramide, loperamide, artemether/lumefantrine, and cefixime, which is empiric therapy for potential malaria or bacterial coinfection. During air evacuation to the United States, he received intravenous fluids, ondansetron, and loperamide.

The patient was transported to the Nebraska Biocontainment Unit 6 days after first symptoms occurred. On admission, the patient had a temperature of 39.2°C, blood pressure of 118/59 mm Hg, and relative bradycardia (87 beats per minute). He had several signs and symptoms characteristic of the early gastrointestinal phase commonly seen during the first week of EVD—fever, chills, myalgia, weakness, malaise, fatigue, nausea, diarrhea, and decreased appetite. Physical examination revealed bilateral conjunctivitis, diffuse nonpruritic macular rash over the chest, and hyperactive bowel sounds, but no abdominal tenderness. The results of the laboratory tests showed the following abnormalities: hyponatremia (sodium level, 131 mmol/L), hypochloremia (chloride level, 99 mmol/L), hypomagnesemia (magnesium level, 1.4 mmol/L), hypocalemia (calcium level, 8.3 mmol/L), hypoaalbuminemia (albumin level, 3.2 g/dL), creatinine (1.03 mg/dL), bicarbonate (26 mmol/L), and no anion gap (6). Aspartate aminotransferase (AST; 362 U/L), alanine aminotransferase (ALT; 114 U/L), and alkaline phosphatase (102 U/L) were elevated, with normal bilirubin (0.2 mg/dL). Thrombocytopenia (64 × 10^3 cells/mL) and mild leukopenia (3200 cells/mL) were present, without anemia (hemoglobin 14.2 mg/dL, hematocrit 41%). Coagulation studies were abnormal with prothrombin time (PT) 16.8 seconds, international normalized ratio (INR) 1.7, and partial thromboplastin time (PTT) 137 seconds. A peripheral blood smear was negative for malaria. On admission, quantitative RT-PCR for EBOV on a blood specimen performed at the Centers for Disease Control and Prevention had a cycle threshold value of 23, reflecting moderately high EBOV load.
Figure 1. Time-course of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and bilirubin relative to day of illness and dosing with brincidofovir and convalescent plasma.

Figure 2. Time-course of white blood cells (WBCs) and platelets relative to day of illness and dosing with brincidofovir and convalescent plasma.
A central venous catheter was placed on admission, and lactated Ringer’s solution was administered. During the next 24 hours, the patient’s condition worsened with vomiting (up to 1500 mL/day), increased diarrhea (up to 3400 mL stool/day), and headache (illness day 7). Tremor of the hands developed 8 days after illness onset; bruising at blood pressure cuff sites and dyspnea with dry cough developed on illness day 9. Chest radiograph taken on illness day 9 revealed bilateral central pulmonary infiltrates consistent with pulmonary edema. Because of severe nausea and anorexia, total parenteral nutrition and intralipids 20% were administered. Severe diarrhea caused hypokalemia and hypomagnesemia, which required treatment with intravenous potassium chloride and magnesium sulfate. Renal function and urine output remained stable. Hypocalcemia was prolonged and correlated with hypoalbuminemia; albumin reached the lowest level on illness day 10 and started increasing by illness day 13. The change in serum levels of bilirubin and hepatic aminotransferases can be seen in Figure 1. Alkaline phosphatase was mildly increased, and remained elevated, possibly secondary to administration of total parenteral nutrition. The patient developed leukocytosis with neutrophilia beginning on illness day 9 and persisting until day 16 (Figure 2). Blood cultures obtained on illness days 6, 9, 12, and 13 were negative. He became anemic on illness day 8 (hemoglobin 12.6 mg/dL, hematocrit 34.3%). Platelet count reached its nadir on day 6 and normalized by day 12 (Figure 2). INR and PT normalized on day 7, and PTT on day 13.

Treatment with brincidofovir (Chimerix, Durham, North Carolina) was initiated after approval by the FDA and the hospital institutional review board, and after obtaining written informed consent from the patient. A 200-mg oral loading dose was administered on illness day 6, followed by 100-mg oral doses on days 9, 13, and 16 (Figures 1–3). On illness day 8, 3 units of convalescent plasma (collected from a recovered EVD patient 77 days after illness onset) were administered.

The presence of EBOV-specific immunoglobulin G (IgG) and immunoglobulin M (IgM) antibodies in the patient’s blood (Figure 3) was measured by enzyme-linked immunosorbent assay [4]. EBOV RNA levels became undetectable on 3 consecutive measurements beginning on illness day 17 [5] (Figure 3). On illness day 20, the patient was discharged home.

**DISCUSSION**

The EVD patient presented had a favorable outcome after receiving supportive and investigational interventions. It is likely that supportive care played a major role, as has been previously reported [6–9]. No results of clinical trials of convalescent plasma treatment for EVD are available, and most published studies are uncontrolled [10] or based on animal models [11–13]. The

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**Figure 3.** Ebola viral RNA dynamics and immunoglobulin titers relative to day of illness and dosing with brincidofovir and convalescent plasma. Abbreviations: EBOV, *Zaire ebolavirus*; IgG, immunoglobulin G; IgM, immunoglobulin M; qRT-PCR, quantitative reverse transcription polymerase chain reaction.
patient’s humoral immune response may have also contributed to recovery as clinical improvement correlated with increases in IgG and IgM titers, but this may also reflect detection of IgM and IgG from the convalescent plasma donor. Previous studies suggest that development of an adaptive humoral immune response is important for survival from EVD [14]. Fatal EVD is characterized by a defective innate immune response, uncontrolled release of inflammatory mediators and chemokines, massive T- and B-lymphocyte apoptosis, and an impaired humoral response with barely detectable EBOV-specific IgG and IgM [14]. Neutralizing antibodies play a crucial role in recovery after EVD through antibody-dependent cell-mediated cytotoxicity, blockage of viral entry, and inhibition of virus budding. Humoral immune responses of EVD survivors have mainly targeted glycoprotein peptides responsible for Ebola virus cell surface attachment and fusion to host cell membranes [14]. Sobarzo et al demonstrated that levels of neutralizing antibodies correlate well with immunoreactivity against the viral proteins nucleoprotein, VP30, and glycoprotein and can persist for up to 10 years after infection [15]. The humoral immune response is primarily directed against nucleoprotein and glycoprotein viral proteins [16]. Emond et al reported successful reduction of the severity of illness with administration of convalescent serum from EVD survivors [6]. It is unknown whether convalescent plasma collected from EVD survivors, which may contain antibodies to EBOV, has any specific benefit for EVD patients as no data from controlled studies are available.

We cannot determine if brincidofovir treatment contributed to clinical recovery. Brincidofovir was developed as a lipid conjugate of cidofovir to improve oral bioavailability and cellular uptake [5]. Cidofovir is predominantly active against double-stranded DNA (dsDNA) viruses. In contrast, EBOV is a nonsegmented, single-stranded, negative-sense RNA virus with distinct structural, functional, and replication properties. The EBOV genome has signal sequences for transcription initiation and termination that contain cytokine and are important for polymerase function [17]. These sequences could be sites for cidofovir incorporation. There are some possible biological explanations if brincidofovir has activity against EBOV: (1) cidofovir may induce apoptosis of EBOV-infected cells arrested in a G1 phase cell cycle; and (2) the incorporation of cidofovir by the viral RNA–dependent RNA polymerases may result in replication inhibition via chain termination or interference with RNA function. Further studies are needed to determine if any specific mechanism of action of brincidofovir exists against EBOV infection.

It has been shown in previous studies of dsDNA viruses that brincidofovir has a safer profile than cidofovir. No significant nephrotoxicity has been described, and the dose does not have to be adjusted for renal function [18, 19]. Cidofovir’s reported side effects are mainly gastrointestinal (typically decreased appetite, diarrhea, and weight loss [19, 20]), symptoms that are generally present in patients with EVD. Prior brincidofovir studies also show elevations in liver enzymes in the first few weeks of therapy, with ALT generally increasing to a greater degree than AST, likely reflecting the effects of cumulative exposure (after ≥2 doses of brincidofovir) [21]. Our patient presented with elevated AST and ALT levels, characteristic of patients with EVD [7, 8], and levels of both enzymes significantly increased before slowly decreasing. Bilirubin was only slightly elevated at the admission.

**CONCLUSIONS**

Although this EVD patient had a favorable outcome, whether convalescent plasma and/or brincidofovir treatment provided any clinical benefit in addition to supportive clinical management is unknown. Any potential therapeutic intervention should ideally be administered as soon as possible. Constraints to timely initiation of therapy include delays from illness onset to when a patient presents at an ETU, and the availability of the therapy. The main tenets of clinical management of EVD remain fluid resuscitation, electrolyte replacement, symptomatic treatment, and provision of organ support for complications. Randomized clinical trials are needed to evaluate new therapies against EVD.

**Notes**

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