2016

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For publication in: Clinical Infectious Diseases (2016) doi: 10.1093/cid/ciw256. First published online: April 26, 2016.

Abstract

From September 2014–April 2015, six persons who had occupational exposures to *Zaire ebolavirus* in West Africa received investigational agents rVSV-ZEBOV or TKM-100802 for post-exposure prophylaxis and were monitored in the U.S. All patients experienced self-limited symptoms after PEP; none developed Ebola virus disease.

Background

Post-exposure prophylaxis (PEP) after Ebola virus (EBOV) exposure can prevent infection or progression to severe Ebola virus disease (EVD) when administered promptly in non-human primates [1, 2]. Whether PEP prevents EVD after EBOV exposure in humans is unknown. Effective PEP is desirable to reduce progression to EVD after EBOV exposures, especially among healthcare personnel (HCP), who have a higher EVD incidence than non-HCP [3].

A few individuals were evacuated from West Africa to the U.S. after potential EBOV exposures and received PEP through FDA-approved emergency Investigation New Drug applications (eIND). Investigational PEP strategies include a recombinant vesicular stomatitis virus vaccine that expresses a *Zaire ebolavirus* surface glycoprotein (rVSV-ZEBOV), a small interfering RNA known as TKM-100802, favipiravir (RNA polymerase inhibitor), and ZMapp (monoclonal antibody cocktail against EBOV glycoprotein).

Limited human data exist about PEP use for potential EBOV exposures and symptoms experienced after PEP administration. Previous reports described rVSV-ZEBOV administration to two physicians and a laboratory worker with percutaneous EBOV exposures [4-6]. One report of HCP medically evacuated to the U.K. after potential EBOV exposure described four individuals given PEP including favipiravir and monoclonal antibody cocktails ZMab, and MIL77 [7]. Of the seven patients described in these case reports who received investigational PEP, none developed EVD. We describe PEP use among six persons monitored in the U.S who experienced potential EBOV exposures during 2014–2015.

Methods

This retrospective case series includes all persons who received PEP after a potential EBOV exposure in West Africa. Exposures included suspected percutaneous exposure to blood or body fluids of an EVD

patient, direct contact with an EVD patient while wearing inappropriate or compromised PPE, or other exposure thought to be of sufficient risk to warrant medical evacuation and consideration of PEP from September 2014–April 2015. Decisions about medical evacuation, whether to initiate PEP, which investigational agent would be used for PEP, the duration of hospital monitoring, and clinical and laboratory monitoring of PEP recipients, were made by clinicians at the treating facilities with input from public health authorities. The rVSV-ZEBOV vaccine was made available under an eIND application to the Food and Drug Administration; the protocol specified a dose of 10^8 pfu. TKM-100802 was also made available under an eIND application. All patients were monitored initially in U.S. healthcare facilities. EBOV nucleic acid testing of blood specimens was performed at USAMRIID using the EZ1 Real-time RT-PCR Assay or at the Centers for Disease Control and Prevention (CDC) using the CDC Ebola Virus NP and VP40 Real-time RT-PCR Assays. Clinicians who cared for PEP recipients were contacted to perform chart review using a standardized form to abstract patient characteristics, EBOV exposures, signs and symptoms after PEP administration, and laboratory results. Data were aggregated and summary results are presented. Data for one case were published previously [4]. This activity was determined to be non-research not requiring an Institutional Review Board determination at CDC.

Results

Six persons received PEP for a potential EBOV exposure assessed to be of sufficiently high risk from September 2014–April 2015. These included three nurses and two physicians who were working in Ebola treatment units (ETUs) when the exposures occurred, and one non-clinician worker (Table 1). All potential EBOV exposures were confirmed or suspected percutaneous exposures that occurred in Sierra Leone; five occurred in ETU patient care areas, and one occurred outside of a nearby ETU (Table 1). Half (3) of injuries involved hollow-bore needles, and two involved broken medication ampules; one injury occurred with an unknown sharp object. One person noticed the injury upon doffing personal protective equipment (PPE); the others recognized the injury immediately. No sharps were known to be contaminated with EBOV; however, the sharp penetrated potentially contaminated PPE in four PEP

recipients. One PEP recipient was not wearing any PPE at the time of injury. Percutaneous injuries occurred while administering medication (3), disposing of sharps (2), and turning a patient with EVD in bed (1). Upon recognizing the injury, all PEP recipients decontaminated the wound site within 15 minutes with a chlorine solution. All were medically evacuated to the U.S. within 2–3 days of injury.

Five patients received rVSV-ZEBOV at a dose of 10^8 pfu in a 1 mL solution; one received multiple TKM-100802 doses at 0.3–0.5 mg/kg daily. Time from EBOV exposure to PEP initiation was 1–3 days. Two began PEP while in West Africa; four began PEP on the medical evacuation flight. HIV post-exposure prophylaxis was given to four individuals; the remaining two declined this intervention.

All PEP recipients were isolated in U.S. healthcare facilities with at least standard, contact and droplet precautions initially; length of stay ranged from 3–19 days. All reported symptoms that began ≤1 day after PEP initiation (Table 2). Of five who received rVSV-ZEBOV, the most commonly reported side effects were fever (4), headache (4), and nausea (4). Fever among rVSV-ZEBOV recipients began 12–24 hours after rVSV-ZEBOV administration. Diarrhea was reported among two rVSV-ZEBOV recipients; diarrhea started 2 days after rVSV-ZEBOV administration for one, and the other had diarrhea that started one day prior to rVSV-ZEBOV administration. One rVSV-ZEBOV recipient vomited 4 days after PEP initiation. One rVSV-ZEBOV recipient developed a rash that appeared one day after PEP initiation and lasted for 18 days. Another rVSV-ZEBOV recipient reported joint pain starting on the day of PEP initiation and resolving by the next day. Three rVSV-ZEBOV recipients reported pain at the injection site. The TKM-100802 recipient developed a fever 48 hours after the first dose and developed redness, swelling, pain, and thrombophlebitis at multiple injection sites. All patients had resolved symptoms upon hospital discharge and were monitored through 21 days after their potential EBOV exposure.

No patients had laboratory evidence of EBOV infection. The EBOV glycoprotein, which is expressed by rVSV-ZEBOV, was detected in blood by RT-PCR in four of five rVSV-ZEBOV recipients. Three rVSV-ZEBOV recipient had detectable IgM and IgG antibodies to EBOV glycoprotein after

vaccination [4]. EBOV glycoprotein was not detected in blood by RT-PCR for the TKM-100802 recipient. Among rVSV-ZEBOV recipients, EBOV nucleoprotein was not detected in blood collected ≥3 days after exposure by RT-PCR. Three rVSV-ZEBOV recipients had RT-PCR for VSV nucleoprotein performed on blood; all had VSV detected.

Discussion

We describe six individuals who received PEP after potential EBOV exposures; none had RT-PCR evidence of EBOV infection and none developed EVD. All patients reported symptoms after PEP administration which may have been attributable to PEP or to other factors, such as anxiety, stress, fatigue related to medical evacuation, or other medications including PEP for HIV.

Safety studies of rVSV-ZEBOV among healthy volunteers have shown that rVSV-ZEBOV is generally well tolerated; early reactogenicity symptoms are common, and rare occurrences of arthritis and vesicular dermatitis have been reported [8-10]. While one of the five rVSV-ZEBOV recipients reported joint pain, none reported arthritis; one person reported a rash. All PEP recipients' symptoms resolved by the time of hospital discharge. An ongoing ring vaccination trial, designed to examine use of rVSV-ZEBOV at a lower dose of 2×10^7 pfu/mL for rapid pre-exposure prophylaxis rather than for PEP [11], may provide additional data on safety, efficacy in prevention of EVD, and duration of protection [12]. Additional vaccine trials that aim to immunize healthcare and other frontline workers prior to an EBOV exposure event are ongoing [13].

Of the few reports of TKM-100802 for treatment of EVD, fever and rigors were described in one patient, the drug was discontinued in another patient due to multi-organ system failure, and a third patient experienced hypotension after the initial infusion [14, 15]. The patient who received TKM-100802 for EBOV PEP experienced fever and injection site reactions, and therapy was stopped after dose 5 of 7 due to these side effects.

This report is subject to limitations. The small number of PEP recipients makes it difficult to generalize any of the clinical findings. PEP was uncontrolled; therefore, we cannot determine whether rVSV-ZEBOV or TKM-100802 were effective in preventing EVD. While the exposures described among PEP recipients were assumed to be high risk for the purpose of public health monitoring, it was not determined whether EBOV exposure actually occurred since no testing was performed on the sharps or PPE to document presence of EBOV.

None of the PEP recipients reported here or previously [4-6] developed evidence of EBOV infection, but it is unknown whether PEP prevented EVD. While the effectiveness of PEP remains unclear from this small case series, high-risk exposures are likely to occur in the future, and timely PEP availability and administration may help in reducing the risk of progression to EVD. Priorities for PEP research include using observational studies or clinical trials when feasible to determine the highest risk EBOV exposures, the optimal time and "window period" for PEP, the safety profile of candidate PEP therapies, and the most effective interventions to prevent EVD after high-risk EBOV exposures.

Notes

Acknowledgments: We thank Bobbie Rae Erickson, MPH, and Amy Schuh, PhD, of the Centers for Disease Control and Prevention (CDC) for assistance with real-time reverse transcription–polymerase chain reaction; the healthcare teams at the Emory Serious Communicable Diseases Unit, the Nebraska Biocontainment Unit, and the National Institutes of Health for the care of these patients; John Beigel (National Institute of Allergy and Infectious Diseases) for facilitating access to PEP for selected patients; Oliver Morgan and Jane Seward (CDC) for their roles in facilitating coordination of those involved in the care of selected patients; and Tekmira, the Public Health Agency of Canada, and New Link Genetics for providing the investigational agents.

Funding: This work was supported by the United States Centers for Disease Control and Prevention. The care of patients at the Emory Serious Communicable Diseases Unit was supported in part by the National Center for Advancing Translational Sciences of the National Institutes of Health (award UL1TR000454). The care of patients at the NIH Clinical Center was funded by the National Institute of Allergy and Infectious Diseases.

Disclaimer: The views expressed are those of the authors, and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Disclosures. Dr. Ströher reports In addition, Dr. Ströher has a patent Recombinant vesicular stomatitis virus vaccines for viral hemorrhagic fevers licensed to NewLink Genetics; Merck & Co., Inc. All other authors have no reported conflicts of interest.

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Table 1: Potential high-risk EBOV exposures experienced by U.S. PEP recipients

Occupation	**Exposure**	**PEP (time from EBOV exposure to initiation)**
Physician	Physician manipulated an intravenous cannula on a viremic EVD patient; while wearing the same gloves, physician drew up medication from an ampule and accidentally stuck needle through both pairs of gloves.	TKM-100802 (2 days)
Nurse	Nurse was providing patient care in an ETU, which included delivering medications and meals and cleaning up bloody emesis and broken glass medication ampules. The nurse did not recognize that an injury had occurred, but during doffing noted a tear in one glove and found a bleeding laceration.	rVSV-ZEBOV (3 days)
Other ETU worker	Worker picked up with bare hands a cardboard box that contained sharps lying in the grass near an ETU that was being renovated. Hollow-bore needle pierced ungloved hand. Unknown whether needle could have been contaminated with EBOV; ETU had not had an EVD	rVSV-ZEBOV (24 hours)

	patient for about 2 weeks.	
Nurse	Nurse broke a glass medication ampule while working in an ETU. The nurse continued to work for about 15 minutes before inspecting gloves; both layers of gloves had been penetrated and blood was noted at the point of penetration.	rVSV-ZEBOV (27 hours)
Physician	A hollow-bore needle that was not contaminated with body fluids from an EVD patient pierced contaminated gloves while physician was disposing of needle in an overflowing sharps container.	rVSV-ZEBOV (43 hours)
Nurse	Nurse felt sharp prick to finger while turning a severely ill EVD patient with an open draining wound; no needle/sharp found. No skin puncture noted initially, but red pin-sized wound found on finger next day.	rVSV-ZEBOV (3 days)

Abbreviations: EBOV, Ebola virus. PEP, post-exposure prophylaxis. EVD, Ebola virus disease. TKM-100802. rVSV-ZEBOV. ETU, Ebola treatment unit.

Table 2: Characteristics, signs, and symptoms of persons receiving post-exposure prophylaxis for potential high-risk EBOV exposures (N=6)

Characteristic	
Male, n (%)	4 (67)
Age, median years (range)	39 (36–45)
Occupational role at time of exposure, n (%)	
Nurse	3 (50)
Physician	2 (33)
Non-healthcare worker	1 (17)
Exposed by percutaneous injury, n (%)	6 (100)
Type of sharp, n (%)	
Hollow-bore needle	3 (50)
Broken medication ampule	2 (33)
Unknown	1 (17)
Sharp and PPE (glove) EBOV contamination status, n (%)	
Non-contaminated sharp through contaminated PPE	2 (33)
Non-contaminated sharp through PPE recently cleaned with chlorine solution	1 (17)
Unknown sharp through contaminated PPE	2 (33)
Unknown sharp, no PPE	1 (17)
Activity at time of sharps injury, n (%)	
Medication administration	3 (50)
Disposing of sharps	2 (33)
Turning patient	1 (17)
Time from exposure to initial decontamination, range	5-15 minutes

Type of PEP received, n (%)	
rVSV-ZEBOV	5 (83)
TKM-100802	1 (17)
Time from exposure to PEP initiation, range	1–3 days
Location of PEP initiation, n (%)	
West Africa	2 (33)
On medical evacuation flight	4 (67)
Time from PEP administration to first sign/symptom, range	10 hours – 2 days

Systemic reactions	**rVSV-ZEBOV (n=5)**	**TKM-100802 (n=1)**
Fever	4	Yes
Highest fever, range °C	37.3–39.1	38.1
Myalgias	3	Unknown
Chills/rigors	3	No
Diaphoresis	3	No
Hypotension	1	Yes*
Malaise	2	No
Fatigue	3	Unknown
Headache	4	Yes
Dizziness	1	No
Arthralgia	1	No
Arthritis	0	No
Rash	1	No
Chest pain	1	No

Dyspnea	1	No
Hypoxia	1	No
Nausea	4	No
Vomiting	1	No
Diarrhea	2	No
Local reactions		
Redness	0	Yes
Swelling	0	Yes
Pain	3	Yes
Thrombophlebitis	0	Yes

* Lowest blood pressure was 90/56 while asleep; resolved without intervention.

Abbreviations: EBOV, Ebola virus. PPE, personal protective equipment. PEP, post-exposure prophylaxis. rVSV-ZEBOV. TKM-100802.