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Preliminary Communication

Emergency Postexposure Vaccination With Vesicular Stomatitis Virus–Vectored Ebola Vaccine After Needlestick

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IMPORTANCE Safe and effective vaccines and drugs are needed for the prevention and treatment of Ebola virus disease, including following a potentially high-risk exposure such as a needlestick.

OBJECTIVE To assess response to postexposure vaccination in a health care worker who was exposed to the Ebola virus.

DESIGN AND SETTING Case report of a physician who experienced a needlestick while working in an Ebola treatment unit in Sierra Leone on September 26, 2014. Medical evacuation to the United States was rapidly initiated. Given the concern about potentially lethal Ebola virus disease, the patient was offered, and provided his consent for, postexposure vaccination with an experimental vaccine available through an emergency Investigational New Drug application. He was vaccinated on September 28, 2014.

INTERVENTIONS The vaccine used was VSVΔG-ZEBOV, a replicating, attenuated, recombinant vesicular stomatitis virus (serotype Indiana) whose surface glycoprotein gene was replaced by the Zaire Ebola virus glycoprotein gene. This vaccine has entered a clinical trial for the prevention of Ebola in West Africa.

RESULTS The vaccine was administered 43 hours after the needlestick occurred. Fever and moderate to severe symptoms developed 12 hours after vaccination and diminished over 3 to 4 days. The real-time reverse transcription polymerase chain reaction results were transiently positive for vesicular stomatitis virus nucleoprotein gene and Ebola virus glycoprotein gene (both included in the vaccine) but consistently negative for Ebola virus nucleoprotein gene (not in the vaccine). Early postvaccination cytokine secretion and T lymphocyte and plasmablast activation were detected. Subsequently, Ebola virus glycoprotein-specific antibodies and T cells became detectable, but antibodies against Ebola viral matrix protein 40 (not in the vaccine) were not detected.

CONCLUSIONS AND RELEVANCE It is unknown if VSVΔG-ZEBOV is safe or effective for postexposure vaccination in humans who have experienced a high-risk occupational exposure to the Ebola virus, such as a needlestick. In this patient, postexposure vaccination with VSVΔG-ZEBOV induced a self-limited febrile syndrome that was associated with transient detection of the recombinant vesicular stomatitis vaccine virus in blood. Strong innate and Ebola-specific adaptive immune responses were detected after vaccination. The clinical syndrome and laboratory evidence were consistent with vaccination response, and no evidence of Ebola virus infection was detected.

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A 44-year-old physician from the United States caring for patients in an Ebola treatment unit in Sierra Leone experienced an unintentional needlestick with an 18-gauge hollow-bore needle that had vented a plastic intravenous bottle. The needle was being placed into a sharps container and inadvertently punctured 2 layers of gloves and caused bleeding of the left thumb. The outer gloves were not visibly soiled but had just been in direct contact with severely ill Ebola patients, including 1 patient with a real-time reverse transcription–polymerase chain reaction (RT-PCR) threshold cycle value of 22, indicating a very high Ebola virus RNA level. Because standard procedures to doff personal protective equipment had to be followed, there was a delay of 10 minutes before decontamination of the wound, which was washed with 0.05% bleach initially, followed by soap and water and 2% chlorhexidine.

To our knowledge, there are no published quantitative data about Ebola virus transmission risk from this type of needlestick. However, use of unsterilized needles for intramuscular injection of medications has been associated in 1 Ebola outbreak with high transmission risk.[1] The patient's exposure was estimated to pose a significant risk of infection.

Postexposure Vaccination

Medical evacuation to the United States was rapidly initiated. Given the concern about Ebola virus disease, a discussion about experimental postexposure vaccination occurred while the patient was in Sierra Leone. The vaccine was available through an emergency Investigational New Drug application and institutional review board approval. The patient provided written informed consent for the vaccine but declined other experimental drugs. A vial of vaccine on dry ice was placed aboard the specialized medical evacuation jet before departure for Sierra Leone.

The vaccine used was VSVΔG-ZEBOV (Public Health Agency Canada and NewLink Genetics Inc), a replicating, attenuated, recombinant vesicular stomatitis virus (serotype Indiana) whose glycoprotein gene was replaced by the Zaire Ebola virus glycoprotein gene (Kikwit strain).[2]

Forty-three hours after exposure, the patient boarded the jet and received VSVΔG-ZEBOV intramuscularly in the right deltoid muscle at a dose of 1×10^8 plaque-forming units in 1 mL of an aqueous solution containing 2.5 g/L of recombinant human serum albumin and 10 mM of tris(hydroxymethyl)aminomethane with a pH level of 7.2. This 1×10^8 plaque-forming units dosage of the clinical lot was chosen because (according to the manufacturer) it was biologically equivalent (due to titering differences) to the 2×10^7 plaque-forming units dosage of the laboratory grade lot used in protective experiments of postexposure vaccination in nonhuman primates.[2,3]

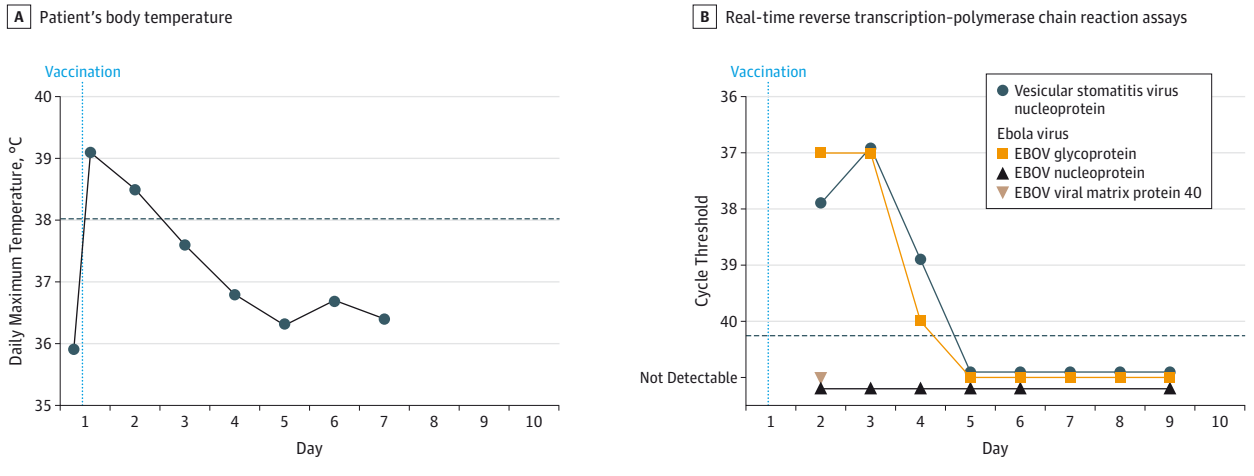
Preceding inoculation, the patient was not taking antipyretic agents and was asymptomatic except for slightly loose stools that he attributed to typical traveler's diarrhea often experienced in Sierra Leone. The patient has written a brief personal perspective on his experience.[4]

Clinical Course

The patient developed malaise and nausea 12 hours later while on the jet, and his oral temperature increased to 38.9°C. He was treated with 975 mg of acetaminophen and 8 mg of ondansetron, both given orally. Given these findings and the Ebola virus concern, the patient donned a full-body Tyvek suit before disembarkation in the United States for ambulance transport to the National Institutes of Health Special Clinical Studies Unit.

Once in the unit, the patient was placed into an isolation room. Health care personnel wore full-contact and respiratory personal protective equipment, including a powered air-

Figure 1. Transient Fever and Low-Level Viremia Postvaccination With VSVΔG-ZEBOV



The VSVΔG-ZEBOV vaccine was made up of a replicating, attenuated, recombinant vesicular stomatitis virus (serotype Indiana) whose surface glycoprotein gene was replaced by the Zaire Ebola virus glycoprotein gene. Prevaccination blood samples were not available. The needlestick occurred 43 hours before vaccination. A, The dashed horizontal line indicates 38°C. B, The number of polymerase chain reaction cycles required to amplify and detect the target RNA is known as the threshold cycle; thus, a lower threshold cycle value indicates that a higher concentration of target template is present.[5] The dashed horizontal line indicates the limit of detection. Further details of real-time reverse transcription–polymerase chain reaction appear in the eMethods section in the Supplement.

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Table. Adverse Events and Laboratory Results Following VSVΔG-ZEBOV Vaccination

	Reference Range	Day[a]							
		1	2	3	4	5	6	7-14	34
Systemic reactions									
Myalgia		3	3	3	2	1	0	0	0
Chills		3	3	1	1	0	0	0	0
Nausea		1	1	1	2	2	0	0	0
Tiredness		3	3	3	2	1	1	0	0
Headache		3	3	3	2	2	0	0	0
Arthralgia		1	1	0	0	0	0	0	0
Local reactions									
Tenderness at injection site		1	0	0	0	0	0	0	0
Pain		0	0	0	0	0	0	0	0
Swelling		0	0	0	0	0	0	0	0
Erythema		0	0	0	0	0	0	0	0
Laboratory values[b]									
White blood cell count, /μL	4230-9070	8550	4000	5730	5580	4970	5150		6550
Hemoglobin, g/dL	13.7-17.5	16.7	15.5	15.9	16.8	15.8	15.4		16
Platelets, /μL	161 000-347 000	198 000	133 000	126 000	124 000	126 000	127 000		255 000
Lymphocytes, /μL	1320-3570	610	930	1830	2370	1890	2000		2150
Creatinine, mg/dL	0.6-1.2	1	1	0.8	0.9	0.6	0.8		1.02
Potassium, mmol/L	3.6-5.1	4.2	5.5	4.9	4.2	5.3	4.3		4.2
Alkaline phosphatase, U/L	42-141	58	51	39	55	44	49		54
Alanine aminotransferase, U/L	10-47	36	31	33	28	25	29		19
Aspartate aminotransferase, U/L	11-38	40	42	51	31	32	33		19
D-dimer, μg/mL[c]	<0.5		0.83	1.07	0.77	0.82	0.97		0.36

Abbreviation: VSVΔG-ZEBOV, a replicating, attenuated, recombinant vesicular stomatitis virus (serotype Indiana) whose surface glycoprotein gene was replaced by the Zaire Ebola virus glycoprotein gene.

SI conversion factors: To convert creatinine to μmol/L, multiply by 88.4; D-dimer to nmol/L, multiply by 5.476.

[a] The patient did not have any prevaccination blood samples taken and did not experience any adverse events prior to vaccination. Day 1 is the day in which the patient was vaccinated. The patient completed a diary card for grading his postvaccination adverse event symptoms on days 1 through 14. The following scoring system was used: 0, none or not present; 1, mild but easily tolerated; 2, moderate but able to tolerate routine activity with effort; and 3, severe and unable to continue routine activity. The values in the Table show the maximum score for each day, but the symptoms may have been to a lesser degree at some point during the day.

[b] Laboratory values for days 7 through 14 are not presented because the patient was asymptomatic after day 6. All clinical laboratory values were normal on day 7 (other than mild increase in D-dimer), and he was discharged on day 10.

[c] Repeated after discharge at a different clinical laboratory; the day 34 level was minimally elevated (normal <0.23 μg/mL). There is no result for day 1 because the test was not performed.

purifying respirator, in accordance with unit policy. Medical history was remarkable for strabismus with monocular vision, tonsillectomy as a child, and intermittent cigarette smoking. Medications at the time of admission were 100 mg/d of doxycycline as malaria prophylaxis, nicotine chewing gum, and the doses of acetaminophen and ondansetron noted above. There was a family history of factor V Leiden, but the patient had no thrombosis history.

Initial physical examination in the unit approximately 14 hours after vaccination revealed the patient to be in mild to moderate distress from fever, nausea, malaise, myalgia, and chills. His blood pressure, pulse, and respiration rate were normal, but he had diminished oxygen saturation (94%) while breathing room air. His maximum documented temperature on vaccination day 1 was 39.1°C (**Figure 1**A). The vaccination site had mild tenderness, and the left thumb wound was visible but had neither erythema nor swelling.

Laboratory testing obtained 15 hours after vaccination revealed absolute lymphopenia (610 lymphocytes/μL) (**Table**). Approximately 18 hours after vaccination, he developed severe myalgia, chills, malaise, and headache (Table). A rapid test for malaria (Binax Now) was negative.

Initial blood real-time RT-PCR results[5,6] were positive at low levels for vesicular stomatitis virus nucleoprotein and Ebola virus glycoprotein and negative for Ebola virus nucleoprotein and viral matrix protein 40 (VP40) (Figure 1B). On day 2, the fever declined (maximum of 38.5°C); however, severe symptoms continued along with mild nausea and arthralgia (Table). Mild lymphopenia persisted (930 lymphocytes/μL) and was associated with thrombocytopenia (133 000 platelets/μL), leukopenia (4000 white blood cells/μL), and mildly elevated level of D-dimer (0.83 μg/mL) (Table). Oxygen saturation ranged between 94% and 96%.

On days 3 through 5, he had progressive resolution of symptoms and laboratory abnormalities (Table). Oxygen saturation increased and ranged between 97% and 99%. The results from real-time RT-PCR for vesicular stomatitis virus nucleoprotein and Ebola virus glycoprotein remained positive on days 3 and 4, but with threshold cycle values increasing from 37 to 40, indicating less viremia. The results from real-time RT-PCR for Ebola virus nucleoprotein (Figure 1B) and for antibodies against the Ebola virus VP40 matrix protein (not shown) were repeatedly negative.

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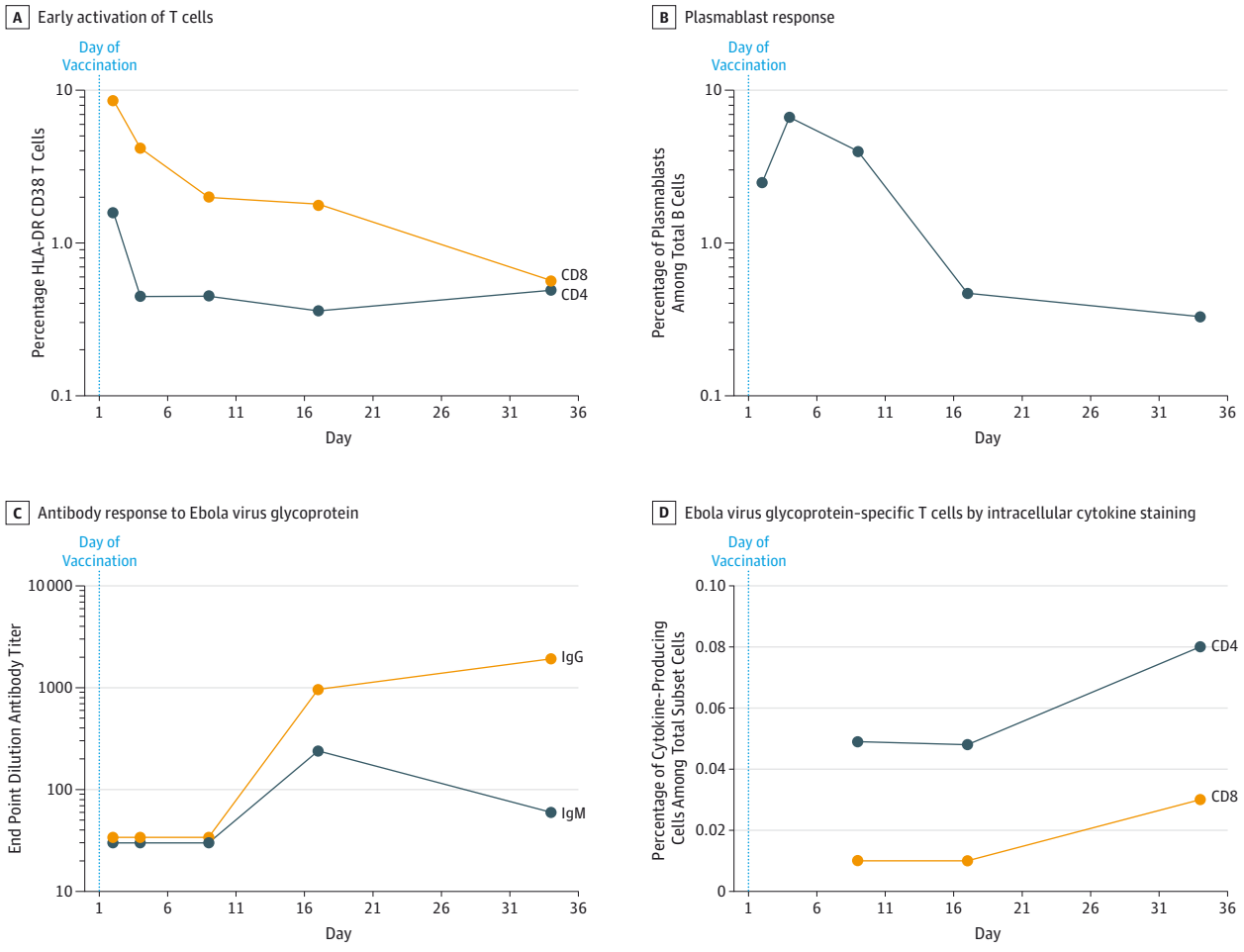
Figure 2. Immune Responses From Assays Conducted on Days 2, 4, 9, 17, and 34



A, Determined by phenotyping using multicolor flow cytometry. B, Plasmablast response determined with multicolor flow cytometry.[7,8] The plasmablasts are $CD3^-/CD20^{-/low}/CD19/CD27^{high}/CD38^{high}$; the B cells are $CD3^-/CD20/CD19$. C, The antibody response to Ebola glycoprotein is shown. Antibody to viral matrix protein 40 IgG was not detectable at all 5 time points assayed (not shown). D, Production of cytokines (INF-γ, tumor necrosis factor, IL-2, or some combination) by glycoprotein-specific T cells after peptide stimulation as measured by intracellular cytokine staining.

Mild pleuritic chest pain occurred on day 4. Chest radiograph was normal and electrocardiogram demonstrated sinus bradycardia (56 beats/min) and incomplete right bundle-branch block known to be preexisting. By day 7, he was completely asymptomatic. When the real-time RT-PCR result was negative for Ebola virus nucleoprotein on day 9, the state health department, in consultation with the US Centers for Disease Control and Prevention, agreed that the patient could complete the 21-day isolation period at home. This period was remarkable for 2 episodes of moderate motion sickness while driving to or from the clinic on days 10 and 17. The patient later returned to work and was doing well 4 months later.

Immune Responses

T-Cell and Cytokine Responses

Activated T cells with increased expression of HLA-DR and CD38[9,10] peaked on day 2 (**Figure 2**A and eFigure in the Supplement). Ebola glycoprotein-specific T cells that produced IFN-γ, IL-2, or tumor necrosis factor, or some combination (higher for CD4 than for CD8 T cells) were identified by day 34 (Figure 2D). The levels of 63 plasma cytokines, chemokines, and growth factors were measured (**Figure 3**); 15 cytokines were undetectable and appear in the eTable in the Supplement. Prevaccination samples were unavailable for this emergency patient; the samples from day 34 were used to normalize the protein levels (Figure 3).

On day 2, the levels of 8 proteins were more than 20-fold higher compared with day 34, and the levels of 28 other proteins were more than 3-fold higher. The anti-inflammatory IL-1 receptor antagonist was 92-fold higher on day 2 compared with day 34. Although IL-1α was not detected, IL-1β was 12-fold higher on day 2 compared with day 34.[11] For the chemokine CXCL10 (IP-10), the day 2 level was 42-fold higher compared with day 34. Therefore, coincident with vesicular stomatitis virus viremia, there was strong activation of innate mechanisms that might function in reactogenicity or as potential protective mechanisms, or both.

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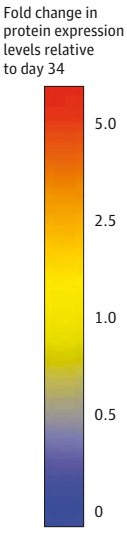
Figure 3. Levels of 48 Detected Plasma Cytokines, Chemokines, and Growth Factors After Vaccination



Cytokines	Day 2	4	9	17	34
IL-1 RA	91.74	1.00	1.00	1.00	1.00
IL-13	23.63	1.00	1.00	1.00	1.00
IL-27	21.32	5.06	2.25	4.04	1.00
IL-22	12.82	5.76	3.34	8.91	1.00
IL-1β	12.26	4.96	4.30	5.44	1.00
IFN-α	6.48	1.89	1.89	1.70	1.00
IL-17α	4.88	2.52	2.35	2.97	1.00
Leptin	4.22	2.04	1.77	1.38	1.00
GM-CSF	4.14	1.77	1.57	1.38	1.00
IL-18	3.99	2.06	1.84	1.30	1.00
IL-10	3.45	2.00	1.84	2.42	1.00
IL-7	3.17	3.18	2.24	1.12	1.00
IFN-γ	3.14	1.62	1.63	1.60	1.00
sCD40L	3.09	1.15	0.95	1.69	1.00
IL-12 P70	2.91	1.60	1.47	1.33	1.00
G-CSF	2.64	1.27	1.20	1.27	1.00
IL-15	2.62	1.70	1.71	1.75	1.00
IL-4	2.58	1.15	1.16	1.30	1.00
IL-12 P40	2.53	1.09	1.14	1.22	1.00
LIF	2.13	1.21	1.18	1.67	1.00
Resistin	2.08	0.85	0.85	1.00	1.00
IL-2	1.84	1.16	1.10	1.45	1.00
IFN-β	1.65	0.91	0.87	1.28	1.00
SCF	1.31	1.12	1.12	0.92	1.00
IL-17F	1.17	0.82	0.85	1.20	1.00
TNF	0.92	0.90	0.91	0.95	1.00
PAI-1	0.76	0.78	0.87	0.74	1.00

Chemokines	Day 2	4	9	17	34
CXCL10	41.92	4.71	3.23	2.35	1.00
MIP-1β	27.76	1.00	1.00	1.19	1.00
MIP-1α	22.58	1.82	1.22	4.07	1.00
TRAIL	9.07	1.09	1.68	2.75	1.00
MCP-1	5.92	1.59	1.12	0.90	1.00
RANTES	4.06	3.11	3.35	1.62	1.00
CXCL9	3.91	1.62	1.45	1.71	1.00
MCP-3	2.23	1.29	1.43	1.48	1.00
sICAM-1	2.08	0.93	0.98	1.09	1.00
Eotaxin	1.77	0.94	1.04	0.82	1.00
SDF-1α	1.43	0.69	0.72	0.88	1.00
sVCAM-1	0.57	0.45	0.66	0.86	1.00

Growth Factors	Day 2	4	9	17	34
EGF	37.75	14.00	2.25	1.00	1.00
TGF-β	24.60	7.24	2.25	3.36	1.00
VEGF-D	7.96	4.68	4.71	1.57	1.00
VEGF-A	7.04	1.54	1.86	1.39	1.00
PDGF-BB	5.26	3.67	2.31	0.83	1.00
TGF-α	3.39	1.28	1.02	1.35	1.00
bNGF	3.06	1.93	1.72	2.39	1.00
BDNF	2.04	2.38	1.70	0.77	1.00
HGF	1.95	1.08	1.04	1.24	1.00

Day 2 was the day after vaccination. The numbers shown within each cell are fold increases (or decreases) relative to the level at day 34. The proteins were detected by antibody-bound beads and quantitated using a Luminex instrument. All protein levels were normalized to day 34 levels because a prevaccination plasma sample was not available. Fifteen additional cytokines were undetectable (eTable in the Supplement). BDNF indicates brain-derived neurotrophic factor; bNGF, β-nerve growth factor; EGF, epidermal growth factor; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; HGF, hepatocyte growth factor; LIF, Leukemia inhibitory factor; MCP, monocyte chemotactic protein; MIP, macrophage inflammatory protein; PAI-1, plasminogen activator inhibitor 1; PDGF-BB, platelet-derived growth factor BB; RA, receptor antagonist; RANTES, regulated on activation normal T cell expressed and secreted; sCD40L, soluble CD40 ligand; SCF, stem cell factor; SDF-1α, stromal cell-derived factor 1α; sICAM-1, soluble intercellular adhesion molecule 1; sVCAM-1, soluble vascular adhesion molecule 1; TGF, transforming growth factor; TNF, tumor necrosis factor; TRAIL, tumor necrosis factor–related apoptosis-inducing ligand; VEGF, vascular endothelial growth factor.

B-Cell and Antibody Responses

Plasmablasts were increasing on days 2 and 4 and decreasing on day 9 (Figure 2B). Serum IgM against Ebola virus glycoprotein[12] was detected on day 17 (titer of 240) and was decreasing on day 34 (Figure 2C). Serum IgG against Ebola glycoprotein was also first detected on day 17 with a titer of 960 that increased to 1920 on day 34.

Discussion

At the time of the patient's vaccination, administration of VSVΔG-ZEBOV had been reported for only 1 human. In 2009, a laboratory worker who had a percutaneous Ebola virus exposure (considered by the authors[13] to be at low but real risk)

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was vaccinated at 48 hours after exposure with 5×10^7 plaque-forming units of laboratory-grade VSVΔG-ZEBOV. Transient fever and myalgia developed after 12 hours, but there was no evidence of Ebola virus infection.

In the current patient, a self-limited, moderate to severe clinical syndrome began at 12 hours after vaccination. Future decision making about using this experimental vaccine for postexposure vaccination will need to balance the risks of harm from the vaccine or possible Ebola infection (both were unknowns at the time of the patient's exposure) against the possible benefit of vaccination (also unknown at the time of the patient's treatment). The patient in this case report experienced more reaction to the vaccine than did the patient in 2009,[13] which may or may not be typical.

Multiple early-phase clinical trials evaluating VSVΔG-ZEBOV were initiated in 2014 after we treated this patient; however, the results are unpublished (eg, ClinicalTrials.gov identifiers: NCT02283099, NCT02287480, NCT02269423, and NCT02280408). Due to the ongoing morbidity and mortality from the current Ebola epidemic in West Africa and using unpublished information on the safety and immunogenicity from the early-phase trials, an efficacy trial of VSVΔG-ZEBOV for preexposure prevention of Ebola in Liberia began in early 2015.[14]

In the current patient, blood real-time RT-PCR results were transiently positive for vesicular stomatitis virus nucleoprotein and Ebola virus glycoprotein genes, but were consistently negative for Ebola virus nucleoprotein gene, which is compatible with detection of VSVΔG-ZEBOV viremia. The patient developed antibodies to Ebola virus glycoprotein, which is in the vaccine, but not against Ebola virus VP40, which is not in the vaccine. Taken together, the evidence is consistent with vaccination response without Ebola virus infection. Neither the safety nor the efficacy of the VSVΔG-ZEBOV vaccine for postexposure protection can be learned from this single case, but the clinical and laboratory parameters are informative at a time when there is a need to garner all information available on Ebola vaccines.

Administration of VSVΔG-ZEBOV was shown to be protective and safe in immunocompromised nonhuman primates infected with simian immunodeficiency virus.[15] In addition, VSVΔG-ZEBOV given 30 minutes after challenge in nonhuman primate models with a uniformly fatal dose of Ebola virus resulted in a survival rate of 50%; 25% survived when it was given 45 minutes postchallenge.[2,3] Small, interfering RNAs[16] and monoclonal antibodies[17,18] also have been shown to protect nonhuman primates when used postexposure. The mechanism of VSVΔG-ZEBOV postexposure protection in nonhuman primates is unknown[2] but has been postulated to be viral interference, stimulation of innate immunity, a receptor blockade of Ebola virus entry by vaccine-encoded Ebola glycoprotein, or a combination of these 3, along with emerging adaptive immunity.[3]

On days 2 and 4, elevated levels of multiple plasma cytokines and chemokines were detected. It is unknown if a strong inflammatory response induced by VSVΔG-ZEBOV would be helpful or harmful in an exposed patient incubating Ebola virus. One hypothesis is that the observed high (anti-inflammatory) IL-1 receptor antagonist level could temporize the cytokine storm induced by the Ebola virus and the observed chemoattractant CXCL10 (IP-10) could mobilize early innate defenses. Vesicular stomatitis virus is a strong inducer of innate responses through toll-like receptors 3, 4, 7, and 13.[2,19] Mouse studies suggested that natural killer cells play a role in the vaccine-mediated protection of VSVΔG-ZEBOV.[20] Systems biology studies of early immune responses are needed to understand the possible mechanisms of postexposure protection in nonhuman primates.

Although 1 of the 2 promising Ebola vaccine candidates, the safety and efficacy of VSVΔG-ZEBOV are unknown. The appropriate dosing to maximize immunogenicity but minimize reactogenicity is yet to be determined. If used as a postexposure investigational agent, vaccination should be given soon after exposure, although the window period is unknown. The Ebola virus incubation period following injection using unsterile syringes and needles,[1,21] and potentially after needlesticks, may be shorter than for person-to-person contact.

A vaccine-induced febrile syndrome may complicate clinical care, and hospitalization may therefore be necessary, following recommended infection-control precautions. Real-time RT-PCR that only targets Ebola virus glycoprotein is expected to yield a positive result briefly postvaccination. Therefore, PCR primers that target other Ebola virus genes should also be used. Systematic data collection is needed to inform future use of this investigational vaccine and would be facilitated by standardized open-label protocols. In the context of these protocols, regional stockpiling of VSVΔG-ZEBOV near facilities where personnel have ongoing potential for occupational exposures might possibly be helpful.

Conclusions

It is unknown if VSVΔG-ZEBOV is safe or effective for postexposure vaccination in humans who have experienced a high-risk occupational exposure to the Ebola virus, such as a needlestick. In this patient, postexposure vaccination with VSVΔG-ZEBOV induced a self-limited febrile syndrome that was associated with transient detection of the recombinant vesicular stomatitis vaccine virus in blood. Strong innate and Ebola-specific adaptive immune responses were detected after vaccination. The clinical syndrome and laboratory evidence were consistent with vaccination response, and no evidence of Ebola virus infection was detected.

ARTICLE INFORMATION

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Author Contributions: Drs Lai and Mulligan had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Lai and Davey contributed equally.
Study concept and design: Lai, Davey, Beck, Rogers, Rubinson, Mulligan.
Acquisition, analysis, or interpretation of data: Lai, Davey, Beck, Xu, Suffredini, Palmore, Kabbani, Kobinger, Ströher, Wolcott, Dorman, Uyeki, Feldmann, Lane, Mulligan.
Drafting of the manuscript: Lai, Davey, Suffredini, Rubinson, Wolcott, Uyeki, Mulligan.
Critical revision of the manuscript for important intellectual content: All authors.
Administrative, technical, or material support: Lai, Davey, Beck, Xu, Suffredini, Palmore, Kabbani, Alimonti, Link, Ströher, Wolcott, Dorman, Uyeki, Feldmann, Mulligan.
Study supervision: Lane, Mulligan.

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