Emergency Treatment for Exposure to Ebola Virus
The Need to Fast-track Promising Vaccines

Thomas W. Geisbert, PhD

Ebola virus is among the most deadly pathogens, with case fatality rates of up to 90%. Ebola virus is categorized as a tier 1 pathogen by the US government because of its potential for deliberate misuse with significant potential for mass casualties. The current outbreak of Ebola virus in West Africa with more than 23,000 cases and 9000 deaths also demonstrates the long-underestimated public health threat that Ebola virus poses as a natural human pathogen. There are no licensed vaccines or postexposure treatments for combating Ebola virus. However, substantial progress has been made in developing vaccines and antivirals that can protect laboratory animals against lethal disease. Advancing these interventions for human use is a matter of utmost urgency.

In this issue of JAMA, Lai et al report the use of a first-generation recombinant vesicular stomatitis virus–based Ebola vaccine (VSVΔG-ZEBOV) to treat a physician who experienced a needlestick in an Ebola treatment unit in Sierra Leone during the current Ebola virus outbreak. A single dose of the VSVΔG-ZEBOV vaccine was administered approximately 43 hours after the potential exposure. The patient experienced a transient febrile syndrome after vaccination. Importantly, no evidence of Ebola virus infection was detected, and the vaccine elicited strong innate and Ebola virus–specific adaptive immune responses. Most significantly, the vaccine, which expresses the surface glycoprotein of Ebola virus, was able to induce an IgG antibody response against the Ebola virus glycoprotein at a level that has been associated with protection of nonhuman primates.

It is difficult to draw any definitive conclusions from a single case report. The inability to detect evidence of Ebola virus infection most likely is because there was not an actual exposure; however, it cannot be completely ruled out that the intervention was effective in controlling Ebola virus replication. Even though this patient experienced some adverse events after vaccination, the patient reported having traveler’s diarrhea prior to receiving the VSVΔG-ZEBOV vaccine; therefore, it is also not possible to draw any strong conclusions regarding any adverse events from this case in regard to the safety of the vaccine. This is the second time that the VSVΔG-ZEBOV vaccine has been used to treat a potential exposure to Ebola virus. The initial use occurred in 2009 for a laboratory worker in Germany and also involved a needlestick injury. The results of that incident were nearly identical; however, the severity of adverse events following vaccination was less notable in the German case compared with the patient in the case report by Lai et al.

The 2 incidents involving the use of the VSVΔG-ZEBOV vaccine for the treatment of high-risk Ebola virus exposures further reinforce the need for public health approaches that prevent and control outbreaks. Efforts to develop effective vaccines and treatments against Ebola virus began soon after its discovery in 1976. However, advances were slow until the decade of the 2000s when at least 10 different preventive vaccines were developed that conferred complete protection in the criterion standard nonhuman primate models. Postexposure treatments and therapies that can protect nonhuman primates against Ebola virus have been much more difficult to develop.

Similar to the rabies vaccine, the VSVΔG-ZEBOV vaccine can be used both as a conventional preventive vaccine and as a postexposure treatment. When used as a treatment, the VSVΔG-ZEBOV vaccine protected 50% of nonhuman primates against lethal Ebola virus (Zaire species) infection when given shortly after exposure.

Only 2 potential therapies, ZMapp and TKM-Ebola, have been shown to completely protect 100% of nonhuman primates from a lethal Ebola virus (Zaire species) infection when administered after exposure. Both drugs have been administered under compassionate use during the current outbreak to treat a number of patients repatriated to Europe and the United States. Even though these patients have had very high survival rates, the role of ZMapp and TKM-Ebola in the outcome is unknown because in many cases they received multiple types of experimental therapies, including convalescent serum, and also likely benefited from the advanced supportive medical care in specialized facilities. Other treatments such as brincidofovir and favipiravir also have been used to treat patients infected with Ebola virus during the current outbreak; however, their benefit is even more difficult to measure because neither treatment has been associated with strong protection of nonhuman primates against Ebola virus.

An important point noted in the report by Lai et al is that the patient declined other experimental drugs in lieu of the VSVΔG-ZEBOV vaccine. This also raises issues regarding patient consent and the use of experimental therapies. This is an important consideration because ultimately the patient or a representative of the patient makes the decision and should be informed of all options, available data, and risks. It is unknown what other drugs were offered to the patient in the report by Lai et al. Shortages of ZMapp during the current Ebola virus outbreak have been reported, and it is clear that even though promising antivirals have been developed, they have
yet to be produced at levels sufficient for the large numbers of cases associated with an outbreak of this magnitude.

The need for antiviral treatments for Ebola virus infection is unquestionable, and stockpiles of ZMapp and TKM-Ebola are critically needed. However, the most effective way to prevent and control outbreaks and to protect high-risk personnel, including medical staff and laboratory workers, is through the use of preventive vaccines along with use of appropriate personal protective equipment. Historically, there has been a small global market for developing an Ebola virus vaccine and there was no financial interest for large pharmaceutical companies to become involved. The current epidemic has spurred substantial scientific activity to develop vaccines.

Companies, including GlaxoSmithKline, Merck, and Johnson & Johnson, are attempting to fast-track the licensure of several Ebola virus vaccines. Phase 1 trials have been initiated, and trials at some test sites have been completed for the GlaxoSmithKline chimpanzee adenovirus-based Ebola virus vaccine and the first-generation Merck-acquired VSVΔG-ZEBOV vaccine. It is encouraging that these large pharmaceutical companies have joined the campaign to address Ebola virus vaccines. It is encouraging that these large pharmaceutical companies have joined the campaign to address Ebola virus, but small biotech firms also have made important contributions.

Moreover, much of the progress during the last decade is a direct result of basic research and early-stage product development funded by the US government, including the Department of Defense, the National Institute of Allergy and Infectious Diseases, and the National Institutes of Health, in particular the Partnerships for Biodefense Program, which has been instrumental in the development of many of the lead candidate interventions.

Reports to date suggest that some adverse events could be associated with the VSVΔG-ZEBOV vaccine, which is not unusual because this vaccine uses a replication-competent virus. Profectus Biosciences has developed a novel next-generation vesicular stomatitis virus-based Ebola virus vaccine that has been engineered for enhanced safety and has been shown to confer complete protection of nonhuman primates against Ebola virus.10 Phase 1 trials are also expected soon with the newer Profectus vaccine and it may prove to be safer than the first-generation vaccine candidate.

In addition to Profectus, other companies, including Novavax, are moving forward with Ebola virus vaccine candidates. Having a variety of competing vaccines should mitigate risk and ensure that in the near future an effective licensed Ebola virus vaccine will be available for human use. Even though vaccination of large populations in endemic areas in Africa may not be practical, vaccination of medical staff and first responders will be of value, particularly because medical staff have been at high risk for infection in the current Ebola virus outbreak. In addition, ring vaccination strategies can be valuable in controlling outbreaks, particularly if rapid-acting single-injection vaccines, such as the vesicular stomatitis virus-based Ebola virus vaccines, are available.

Although it is not possible to know with absolute certainty whether the first-generation VSVΔG-ZEBOV vaccine used to treat the potential high-risk exposure had any influence on survival of the exposed patient in the report by Lai et al,4 this incident serves as an example of how important it is to have safe and effective countermeasures available in sufficient quantities that can be rapidly deployed for emergency use for both medical workers and affected populations.