Vaccines Against Ebola and Marburg Viruses Show Promise in Primate Studies

Tracy Hampton, PhD

As naturally deadly pathogens that could also be manipulated for use as agents of bioterrorism, the Ebola and Marburg viruses are threats that researchers have sought to overcome for decades.

While there are no approved vaccines or therapies against these pathogens and the often fatal hemorrhagic fevers they cause, a report published July 5 in an online edition of *Nature Medicine* describes new and promising vaccines that appear to offer complete protection for nonhuman primates infected with the viruses (http://www.nature.com/naturemedicine).

**THE FIGHT AGAINST FILOVIRUSES**

At press time, the largest and deadliest recorded outbreak of Marburg virus was still ongoing in Angola, with 422 cases reported as of June 17 (356 of which were fatal). Updates of the outbreak can be found at http://www.who.int/csr/don/en/. Ebola virus, a member from the same family (Filoviridae) as Marburg, has also caused significant outbreaks in Africa during the past 3 decades. While Ebola has had a higher profile with respect to natural outbreaks and the potential use of the virus as an agent of bioterrorism, Marburg poses a similar threat, said lead author Steven Jones, PhD, of the Public Health Agency of Canada, in Winnipeg, Manitoba.

"It just doesn’t get the big press that Ebola does despite the fact that it was Marburg that the former Soviet Union decided to weaponize," he said. Jones and his colleagues have therefore been studying both Ebola and Marburg viruses over the years with the hope of developing a vaccine strategy to protect against both of these pathogens.

In their new report, the investigators described the design and testing of vaccines based on a live attenuated recombinant form of the vesicular stomatitis virus (VSV) genetically engineered to express either the Ebola or the Marburg virus surface protein. The researchers chose VSV as a vector because humans do not have strong preexisting immunity to this virus, which is not the case for other viral candidates such as adenovirus, a familiar cause of the common cold. Preexisting immunity to a viral vector can reduce the efficacy of vaccination.

"Hardly anybody has antibodies against VSV," said principal investigator Thomas Geisbert, PhD, of the United States Army Medical Research Institute of Infectious Diseases, in Fort Detrick, Md. "And even if they did, it probably wouldn’t be much of a problem," he added, because the most immunogenic component of VSV, the G-surface protein, was not included in the vaccine.

Geisbert also explained that the rationale for using a live vaccine rather than a killed one is the belief by many researchers that a live vaccine may be needed to provide durable protection against these agents. For health care and laboratory workers, as well as individuals in remote areas who may be at high risk and have limited access to medical care, “you’re not necessarily going to want to boost a person every year or two,” he said. The researchers have reason to believe that the vaccine under study may prove to be effective over time and not subject to resistance emerging in evolving virus strains. For example,
viruses in the 1976 and 1995 Ebola outbreaks were found to be virtually the same; in this study, the vaccine was made using Ebola glycoprotein from the 1976 strain and the animals were challenged with the 1995 strain.

FROM MONKEYS TO HUMANS

In their research with 12 macaques, Geisbert and Jones demonstrated that when given a single intramuscular injection of either vaccine, animals were completely and safely protected when the corresponding virus was administered at a typically lethal dose. They also found no evidence of viral replication in any of the vaccinated animals.

Injection with the Ebola vaccine induced strong cellular and antibody-mediated immune responses while the Marburg vaccine induced a stronger antibody-mediated than cellular response. While this may be an important finding, the researchers are not ready to draw any conclusions and are using more sensitive laboratory tests to see if the initial results hold up.

As the vaccine candidates were found to be safe and effective, they warrant testing in humans, according to the investigators. The next steps include improving the vaccines and determining the proper dose. For example, there are two species of Ebola virus that are known human pathogens but the current Ebola vaccine protects against only one of them. Therefore, Jones is working on inserting a gene specific to the second species into the vaccine.

In addition, finding the lowest effective dose will be important for safety and production issues. The doses given in the study were high, but based on mouse studies, the researchers believe that lower doses will offer protection as well. The investigators also hope to develop a vaccine that could be administered orally or intranasally rather than intramuscularly.

Also planned are studies to test if the vaccines can prevent disease even if given after exposure to the viruses. Effective post-exposure vaccines would be vital tools not only for those exposed during an Ebola or Marburg outbreak but also for researchers who risk exposure in the laboratory. “We’re interested in that for both altruistic and entirely selfish reasons,” said Jones.

Experts Promote Adoption of Chest Pain Guidelines by Emergency Departments

Mike Mitka

ALTHOUGH RAPID ASSESSMENT BY emergency physicians is vital in treating patients presenting with chest pain and other signs of acute coronary syndrome, the ambiguity surrounding symptoms can delay or result in suboptimal treatment. While guidelines to help physicians in this task were created in 2002, they have not been widely adopted.

To address this situation, the American Heart Association (AHA) and the Society of Chest Pain Centers issued a scientific statement on May 24 offering some practical measures to help emergency physicians incorporate established, evidence-based guidelines to quickly evaluate and treat unstable angina/non–ST-segment elevation myocardial infarction (UA/NSTEMI) into clinical practice. These include templates for forms that can be used in the emergency department to evaluate patients with chest pain, an algorithm to speed assessment, and a standing order set to improve use of approved therapies (Gibler et al. Circulation. 2005;111:2699-2710).

W. Brian Gibler, MD, chairman of the AHA writing group that issued the statement, said the document was needed because guidelines issued in 2002 had yet to disseminate through the medical community.

“It was very clear that [the guidelines] were not being used as regularly as we thought they should,” said Gibler, professor and chairman of the department of emergency medicine at the University of Cincinnati College of Medicine. “We felt that through this statement we could offer a practical element, not only for emergency physicians but for cardiologists throughout the country.”

Each year, more than 5.3 million patients present to US emergency departments with chest discomfort and related symptoms, of which about 1.4 million are hospitalized for UA/NSTEMI. For a variety of reasons, these patients are not always getting the proper assessment and treatment at the correct time. As examples, Gibler cited studies showing that while β-blockers should be used in about 95% of the patients with UA/NSTEMI, only 60% of patients in some hospitals receive them. The same disparities were seen in the administration of glycoprotein IIb/IIIa inhibitors and clopidogrel, Gibler said.

A JOINT EFFORT

The scientific statement is not meant to be an edict or criticism handed down by the AHA, said Gibler, who noted that the group that drafted it was made up of an equal number of emergency physicians and cardiologists. The statement will also be published in August in the Annals of Emergency Medicine, the journal of the American College of Emergency Physicians.

“[Physicians] all want to do the right thing, but when you have 15 to 20 things to do for a patient in a very short