

Antiviral compound protects nonhuman primates against Marburg virus

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An experimental drug that protected monkeys from the deadly Marburg virus appears to have potential for treating people who have been exposed to the virus, according to a study published in the July 23 edition of *The New England Journal of Medicine*. Marburg virus is closely related to Ebola virus and also causes a severe hemorrhagic fever.

The research was jointly conducted by the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) and the biotechnology firm Sarepta Therapeutics, Inc., using a compound known as AVI-7288.

Taken together, the results of efficacy testing conducted in nonhuman primates and safety testing performed in a Phase I clinical trial suggest that AVI-7288 has the potential to be used to treat Marburg [virus](#) infection in humans when administered post-exposure, according to the authors.

Case fatality rates associated with Marburg virus have been reported to be nearly 90 percent and the virus is deemed a potential "Category A" bioterrorism agent by the Centers for Disease Control and Prevention. No licensed vaccine or therapy is currently available for Marburg virus infection.

For over a decade, USAMRIID and Sarepta have been collaborating to develop and test a class of antisense compounds known as phosphorodiamidate morpholino oligomers (or PMOs), according to senior author and USAMRIID Science Director Sina Bavari, Ph.D.

Antisense drugs are designed to enter cells and eliminate viruses by preventing their replication, Bavari explained. The drugs act by blocking the translation of critical viral genetic sequences, preventing a key viral protein from being made and giving the infected host time to mount an immune response and clear the virus. AVI-7288 specifically targets the viral messenger RNA that encodes Marburg virus nucleoprotein.

Led by Bavari and Travis Warren, Ph.D., the USAMRIID team performed a series of studies involving a lethal challenge with Marburg virus in nonhuman primates to determine the efficacious dose and regimen of AVI-7288, as well as to characterize the drug exposures in animals that produced efficacy. *Cynomolgus* macaques were exposed to Marburg virus and then received one of three treatments: AVI-7288, an inactive placebo, or a saline control.

Survival in infected nonhuman primates was dose-dependent, with survival rates of 0%, 30%, 59%, 87%, 100%, and 100% among monkeys treated with AVI-7288 at a dose of 0 mg, 3.75 mg, 7.5 mg, 15 mg, 20 mg, and 30 mg per kilogram of body weight, respectively. In contrast, none of the monkeys treated with placebo or the saline control survived.

In an efficacy study involving nonhuman primates that was specifically designed to evaluate the efficacy of AVI-7288 after delayed treatment, a dose of 15 mg per kilogram per day for 14 days starting at 24, 48, and 96 hours after viral challenge provided 83%, 100%, and 83% protection, respectively. An additional study was conducted in which the AVI-7288 drug levels in Marburg virus-infected monkeys were carefully monitored to determine whether the presence of replicating virus altered systemic drug levels compared to healthy animals.

Next, the Sarepta team designed and conducted a Phase I clinical trial. This study was a randomized, double-blind, placebo-controlled trial designed to characterize the safety, tolerability and pharmacokinetics of

AVI-7288 after daily repeat dosing.

Over 14 days, 40 healthy human volunteers (8 per dose group) received up to 16 mg per kilogram of body weight per day, representing the highest continuous dosing of an antisense agent. This dosing also exceeded the predicted human efficacious dose for AVI-7288 estimated by three different models based upon the nonhuman primate studies that demonstrated up to 100 percent animal survival, including a delayed time-to-treat setting.

"No significant safety concerns or dose-dependent adverse side effects of AVI-7288 were reported with respect to any safety end point evaluated," said Michael Wong, M.D., senior medical director for infectious diseases at Sarepta.

According to Wong, development of AVI-7288 has been conducted according to the U.S. Food and Drug Administration's Animal Rule (Code of Federal Regulations, 21 CFR 314.600). The rule provides a framework for potential licensure of medical products when definitive efficacy studies that would involve exposing healthy human volunteers are unethical and field trials after accidental human exposure are not feasible.

"Results described in this manuscript provide a comprehensive characterization of the efficacy of the PMO antisense platform against Marburg virus in [nonhuman primates](#) and its safety profile in humans," Bavari said. "Importantly, taken together, these results have allowed for detailed modeling to predict a human dose of AVI-7288 that could reasonably be expected to protect humans exposed to Marburg virus."

Marburg virus was first identified in 1967 during an outbreak in Marburg, Germany, when laboratory workers were infected while dissecting African green monkeys from Uganda. Since then, infections

in humans have occurred in Africa, as well as sporadically outside Africa in travelers returning home from that continent. The next Marburg virus outbreak is likely to occur without warning, as has been seen with the recent epidemic in West Africa of the closely related Ebola virus.

Following initial crossover of Marburg virus from host animals to humans, person-to-person transmission may occur through contact with body fluids from a patient or contact with equipment and other objects contaminated with infectious blood or tissues.

Research on Marburg virus is conducted in Biosafety Level 4 (maximum containment) laboratories, where investigators wear positive-pressure "space suits" and breathe filtered air as they work. USAMRIID is the only organization in the Department of Defense with Biosafety Level 4 capabilities, and its research benefits both military personnel and civilians.

USAMRIID's mission is to provide leading-edge medical capabilities to deter and defend against current and emerging biological threat agents. The Institute plays a key role as the lead military medical research laboratory for the Defense Threat Reduction Agency's Joint Science and Technology Office for Chemical and Biological Defense. USAMRIID is a subordinate element of the U.S. Army Medical Research and Materiel Command.

This study was performed under contract with the Joint Product Management Office of BioDefense Therapeutics, a component of the Medical Countermeasure Systems Joint Project Management Office, U.S. Department of Defense, and was also supported by the Defense Threat Reduction Agency.

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