

Use of experimental Ebola drug raises red flags among medical experts

By MONTE MORIN

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Two American aid workers were gravely ill, fighting to survive infection with the deadly Ebola virus. A San Diego drug company had three doses of an experimental Ebola medicine that showed promise in monkeys but had never been tested in humans.

Getting the medication to the two patients in Liberia seemed like the obvious thing to do. Members of the Centers for Disease Control and Prevention, the National Institutes of Health and the Christian aid organization Samaritan's Purse worked together to make it happen.

Patient advocates who believe the drug is helpful are asking when it can be made available to the hundreds of West Africans who are ill.

But what looks like a simple case of humanitarian goodwill could lead to some unintended and very negative consequences, experts said Tuesday.

Although there could be a short-term gain for a dying patient, in the long run it would undermine scientists' ability to determine whether the drug was actually safe and effective.

"I don't think we want to say these drug companies are obligated to suddenly mass-produce these drugs," said Jennifer Blumenthal-Barby, a medical ethicist at Baylor College of Medicine in Houston. "That would subvert the whole FDA-regulated process of trying to do solid research on these drugs."

The Food and Drug Administration has elaborate rules for evaluating drugs before they are approved for widespread use. The process can take years, involving hundreds or thousands of patients and costing drug companies millions of dollars.

The rules are designed to make sure that a medication doesn't make patients more sick than they are and that it fights the disease it was created to fight. They are also used to figure out the minimum dose needed to get the desired effect.

The centerpiece of these rules is the clinical trial, which allows researchers to show that patients who took the drug fared better than patients who didn't.

In this case, there will be no way to tell whether Dr. Kent Brantly and hygienist Nancy Writebol were helped by the experimental Ebola drug, said Dr. Anthony Fauci, head of the National Institute of Allergy and Infectious Diseases.

The two aid workers are being treated in a specialized isolation ward at Emory University Hospital in Atlanta. If they survive their infections, doctors won't know whether it's because of the drug or the other care they receive. The only thing they'll be able to say with certainty is that the drug didn't kill them.

"I do hope that it was effective, but when you're dealing with medicine and all the vicissitudes, you can't say definitively," Fauci said.

Ebola is a virus that causes flu-like symptoms, such as fever, vomiting, aches and intense weakness. As it progresses, patients may suffer serious bleeding, as well as kidney or liver failure.

Experts estimate that it is fatal in 45% to 90% of cases. The outbreak in West Africa has sickened at least 1,603 people and caused 887 deaths, according to the World Health Organization.

The experimental drug given to Brantly and Writebol is a cocktail of three monoclonal antibodies designed to prevent the Ebola virus from latching onto and inserting itself into a host cell. If the virus does enter the cell, it begins to mass-produce copies of itself.

The drug, called ZMapp, is one of several under development to fight Ebola. Allowing any of them to be given to patients without proper vetting would be problematic, said Arthur Caplan, director of the medical ethics division at New York University Langone Medical Center.

"There's a fairly good chance that it could do more harm than good," Caplan said. "The drug could kill you faster, or make you die more miserably."

And Ebola isn't 100% fatal, he said; some patients who might have survived could wind up dying after taking an untested drug.

Even if it seems that patients have nothing to lose, the FDA has argued that its clinical trial system ultimately benefits more patients.

In 2003, a patients' rights group went to court seeking expanded access to experimental drugs for terminally ill patients. The Abigail Alliance argued that patients with "desperate diagnoses" had a constitutional right to potentially lifesaving treatments that had passed an initial round of safety testing.

But that would have removed a powerful incentive for patients to participate in clinical trials, FDA backers argued. A federal appeals court ultimately sided with the FDA, and the Supreme Court declined to hear the case.

There are other problems too. Monoclonal antibody drugs like ZMapp are very expensive to produce, so determining the smallest dose that's still effective is important, Caplan said. That requires proper testing.

Likewise, product liability and payment issues are much more complicated for unapproved drugs. Insurance companies "don't even pay for some things that are already approved," Caplan said. "Paying for things that are experimental is not their thing."

Caplan said he doubted the two Americans would have received the drug if they were in the United States. The FDA does have a **system** for allowing patients with life-threatening conditions to use unproven drugs when they have no other options, but they must get a "compassionate use" waiver and convince the agency that the drug won't present any unnecessary risks.

But Brantly and Writebol did not need such a waiver, because they received the drug in a Liberian hospital, beyond the FDA's jurisdiction.

An FDA spokeswoman said she could not reveal whether Mapp Biopharmaceutical Inc., the company that developed ZMapp, applied for a waiver in this case.

Even if the drug were deemed safe for immediate use and a donor were found to pay for it, it could take months or longer to produce enough to treat everyone who wanted it.

"You'll be in shortage right away and you'll have some hard choices to make about who goes first," Caplan said.

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