

Test of Alzheimer's Vaccine Is Halted

12 Volunteers Said to Be Seriously Ill With Brain Inflammation

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Twelve volunteers inoculated with a highly touted experimental vaccine designed to reverse the course of Alzheimer's disease have fallen seriously ill with brain inflammation, forcing the vaccine's manufacturer to stop giving the shots and raising doubts about the product's clinical potential, according to sources familiar with the study.

The vaccine, made by the Irish pharmaceutical company Elan and known by its code name AN-1792, had generated unusually intense enthusiasm among scientists and patient advocates during the past two years, as experiments in mice suggested it could halt the progression of Alzheimer's and perhaps even cure the deadly disease.

Alzheimer's gradually robs people of their minds. It affects 2 million to 4 million elderly Americans and is expected to affect 15 million by 2030. Even the best treatments today have a very modest impact.

Taking an unprecedented immunologic approach to treating a brain disease, the vaccine aims to elicit an immune system attack against "beta amyloid," the brain protein believed to be at the root of Alzheimer's.

Although animal studies and early human safety studies suggested the vaccine was reasonably safe, the strategy was controversial. Immune reactions typically cause inflammation, and inflammation in the brain can cause serious problems or death.

Company officials have released few details about the problems. A spokesman said an independent committee is reviewing data from the study, which has enrolled about 360 people with mild to moderate Alzheimer's in four European countries and 11 U.S. sites.

But sources familiar with the study, including some who have been in contact with Elan officials, said there is little question the vaccine triggered the brain reactions, which some called encephalitis (an inflammation of the brain) and another called "meningoencephalitis," an inflammation of the brain and surrounding membranes.

Both syndromes can cause symptoms ranging from fever, headache and vomiting to altered consciousness, muscle weakness and seizures.

Some scientists had warned that the vaccine might trigger such complications or even exacerbate Alzheimer's, a disease some believe is caused by natural inflammatory processes.

One such critic, Trey Sunderland, chief of the geriatric psychiatry branch at the National Institute of Mental Health, said yesterday that the vaccine may have caused the encephalitis in volunteers directly or it may have caused a disruption of blood vessels in the brain. That would allow viruses or other infectious agents to enter and cause encephalitis.

Elan, which is developing the vaccine with Wyeth, a pharmaceutical division of American Home Products

Corp. of Madison, N.J., would not say yesterday how quickly it had halted inoculations after the first few patients were diagnosed. The company also would not say what, if any, information was being shared with other volunteers who might be at ongoing risk of encephalitis.

A company spokesman said only doctors at individual test sites could speak to that issue, but officials at several sites yesterday said they had been told by the company not to talk to reporters.

Even when things go well, experts said, clinical trials involving people with cognitive deficits pose extraordinary challenges to the notion of "informed consent" -- the requirement that volunteers be made aware of all the risks of a study and of any changes in those risks during the course of a study.

An Elan spokesman yesterday said the company "follows all appropriate clinical standards to ensure the well-being of all patients in studies and is working closely with their physicians." All those who experienced ill effects "have been treated and are responding appropriately," said the spokesman, who refused to characterize their health further.

The company first mentioned the emerging problem Jan. 18, in a low-profile "update" posted on its Web site. In the second paragraph of the update, the company noted that four patients in the high-profile study had "clinical signs consistent with inflammation in the central nervous system," and that further dosing of patients in the multicenter international trial had been "temporarily suspended." It did not say when the diagnoses were first made.

Since then, the number has climbed to 12, at several test sites, according to sources in contact with Elan officials. One of those, William Thies, vice president of medical and scientific affairs at the Alzheimer's Association, said he still believes the general approach of immunotherapy for Alzheimer's has a promising future, though details of the vaccine might have to change.

Elan has said it is developing products that are similar to AN-1792 but more refined.

"I think everyone is puzzled" about why the problems happened, said Marilyn Albert, an Alzheimer's researcher at Massachusetts General Hospital, who heads the Alzheimer's Association's medical and scientific advisory council. But in all likelihood, Albert said, "they can't go forward with this formulation."

It is the second major setback for Elan this month. The company announced earlier that certain officers and directors were being sued by shareholders alleging violations of U.S. securities laws, and that the company was under investigation by the Securities and Exchange Commission.

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