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Interrupted Alzheimer's vaccine study yields hopeful results, as new clinical trial prepares to open at U-M

Newly published results from prematurely stopped study suggest mental, physical effects from immune system attack on key Alzheimer's protein

ANN ARBOR, Mich. — Training the body's immune system to fight back against Alzheimer's disease may still offer a promising option for slowing or even preventing the tragic brain disorder that affects 4.5 million Americans.

That's the conclusion of two new papers published in the journal *Neurology* by an international team of researchers who vaccinated hundreds of Alzheimer's disease patients with beta amyloid, a protein that builds up in Alzheimer's brains.

The study was stopped early in 2002 after a few participants developed brain inflammation. But the researchers continued to monitor the patients for up to a year after their last injection. The new papers, including one led by the University of Michigan Health System neurologist who headed the study's safety committee, summarize the results of that effort.

Even as those results are published, doctors at U-M are preparing to recruit participants for a phase II clinical trial to test a new Alzheimer's immunotherapy vaccine strategy that has been through a phase I safety trial. The phase II study, which aims to stimulate an immune attack against beta amyloid without raising brain inflammation risk, is being conducted at 30 centers in the U.S. and dosing has already begun at some sites. All the trials have been funded by Elan Corporation and Wyeth Pharmaceuticals.

Results from the interrupted trial show that on the whole, study participants whose immune systems mounted a response against beta amyloid performed significantly better on a series of memory tests than those who received a placebo injection.

Brain scans also showed that patients who had an immune response experienced a decrease in brain size, possibly indicating the removal of built-up protein due to an immune system attack. A smaller group of immune responders also had a decrease in levels of a protein called tau in their spinal fluid, compared with participants who received placebo — possibly indicating a slowing in the death rate of their brain cells.

"The idea of inducing the immune system to view beta amyloid as a foreign protein, and to attack it, holds great promise," says Sid Gilman, M.D., F.R.C.P., the first author on one of the new papers and the head of the Data Safety Monitoring Board for both clinical trials. "We now need to see whether we can create an immune response safely and in a way that slows the progression of Alzheimer's disease and preserves cognition."

— more —

Gilman is the William Herdman Professor of Neurology at the U-M Medical School and director of the Michigan Alzheimer's Disease Research Center, one of 32 in the country funded by the National Institute on Aging.

Nancy Barbas, M.D., M.S.W., a U-M neurologist who will soon begin recruiting participants for the new trial, calls the approach, known as immunotherapy, exciting. "Safety is paramount, given the experience with the last trial, and the new study is designed to be extraordinarily cautious and conservative," she says. "But if we can show an effect, it will mean we're that much closer to giving patients and their families better options for treatment."

Rather than injecting participants with beta amyloid itself, the new trial is based on injections of humanized antibodies against part of the beta amyloid molecule. The antibodies should help trigger the immune system to attack beta amyloid, but will be cleared by the body soon after injection. That means a series of six injections to "remind" the body to attack beta amyloid.

As in the previous study, participants will be randomly assigned to receive either antibodies or a placebo; neither they nor the researchers will know what they got until the 27-month study ends. The new study will enroll 180 adults between the ages of 50 years and 85 years who have a diagnosis of probable Alzheimer's and a caregiver who can bring them to frequent appointments for brain imaging, neuropsychological testing and blood tests. Some participants will have additional blood tests or spinal fluid tests; they will also have a slightly higher chance of getting antibodies.

Gilman explains that the concept of vaccinating against beta amyloid was first proposed by scientist Dale Schenk. In the late 1990s, Schenk and his colleagues showed that vaccination from birth could prevent mental decline in mice that had been bred to develop Alzheimer's-like disease. They and others also showed that older mice receiving the vaccine appeared to regain cognitive function.

The exciting animal research results led to a Phase I trial in humans with Alzheimer's disease that showed no ill effects — and then the Phase II trial that was stopped early.

"With the full agreement of both sponsors, Elan and Wyeth, we halted the study as soon as we heard of the first few cases of meningoencephalitis, or brain inflammation," says Gilman, referring to the trial's Data Safety Monitoring Board of independent experts not involved in treating trial participants. "But for a year afterward, we kept participants and researchers blinded to which patients had received beta amyloid and which had received placebo."

In all, 59 of the 300 participants who received at least one injection of beta amyloid developed significant quantities of antibodies against it in their blood. All but three of these 59 patients, who were called "antibody responders," had received at least two injections before the study was stopped; nine of them had received three injections. Thirteen of the 59 developed some level of encephalitis, as well as five of the patients whose immune systems did not react as strongly.

Although the study showed no statistical difference between the placebo and beta amyloid groups in results on five tests often used in patients with Alzheimer's disease and other dementias, there were significant differences on a battery of other tests that measure memory, executive function and verbal ability. The difference reached statistical significance in immune responders compared with patients who received placebo.

Spinal fluid samples taken from 21 of the participants in the study before it was stopped also reveal some intriguing hints. The 11 immune responders had a significant decline in levels of the tau protein, a structural protein considered a hallmark of cell death in the brain, when compared with 10 participants who received placebo.

Also encouraging, but not conclusive, is evidence from autopsies conducted on Phase I and II trial participants who have died in the years since the studies were completed or stopped, Gilman says. "Three participants died of causes unrelated to the vaccination, two of whom had developed encephalitis and one other did not develop encephalitis. All had large patches of their brains where beta amyloid had apparently been cleared out — the tangles of tau protein were still visible," he explains.

The first three cases from the Phase II trial have been published in separate papers. The fourth case of a patient in the Phase I trial was recently presented at an international meeting. The participant received four injections of beta amyloid and had evidence in the brain tissue of immune system cells (microglia) removing beta amyloid protein — a sign of an active immune response.

The MRI images taken of study participants before and after their injections also showed shrinking of brain tissue that was more pronounced in the 45 immune responders than in 57 placebo patients. “This was the opposite of what we expected, and it’s exciting because it was associated with relative preservation of memory,” says Gilman. “It may be that beta amyloid was taken out of the brain as a result of the immune response, and that the protein carried water with it, causing further shrinkage.”

The new clinical trial builds on the interrupted study’s design, Barbas says, by including MRI and electrocardiogram exams, blood and urine tests, regular vital sign exams, and tests of memory and thinking ability. All of the injections will be in the first year, with the second year for follow-up exams.

The U-M is not yet recruiting participants for this study, but is taking names of those people who might want to be contacted when recruitment opens. U-M researchers are also seeking people who might want to learn about other opportunities to participate in Alzheimer's disease and dementia research at the U-M. Call 734-647-7760 or email neuro-dementrials@med.umich.edu.

The first authors of the two papers in *Neurology* are neurologists who are independent of the two sponsoring companies. Gilman is first author of one paper; the other first author, on the paper detailing MRI results, is Nick Fox of the Dementia Research Centre at the Institute of Neurology in London’s National Hospital for Neurology and Neurosurgery.

Gilman was reimbursed by Elan Corporation for his time reviewing safety data for the interrupted clinical trial, and has the same relationship for the purposes of the new clinical trial. He receives no other funds and no stock or stock options from the sponsors. Other authors of the papers include Elan employees and researchers who have received honoraria from, or hold stock in, Elan and Wyeth.

Citation: Clinical effects of A β immunization (AN1792) in patients with AD in an interrupted trial, *Neurology* ; 64: 1553

Effects of A β immunization (AN1792) on MRI measures of cerebral volume in Alzheimer disease *Neurology* ; 64: 1563

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