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Testing a Drug That May Stop Alzheimer's Before It Starts

By PAM BELLUCK

In a clinical trial that could lead to treatments that prevent Alzheimer's disease, people who are genetically guaranteed to suffer from the disease years from now — but who do not yet have any symptoms — will for the first time be given a drug intended to stop them from developing it, federal officials announced Tuesday.

Experts say the study will be one of only a very few ever conducted to test prevention treatments for any genetically predestined disease. In Alzheimer's research, the trial is unprecedented, "the first to focus on people who are cognitively normal but at very high risk for Alzheimer's disease," said Dr. Francis S. Collins, director of the National Institutes of Health. Most of the study's participants will be drawn from an extended family of 5,000 people who live in Medellín, Colombia, and remote mountain villages outside that city. The family is believed to have more members who suffer from Alzheimer's than any other in the world. Those who possess a specific genetic mutation begin showing cognitive impairment around age 45, and full-blown dementia around age 51. The 300 family members who participate in the initial phase of the trial will be years away from developing symptoms. Some will be as young as 30.

The $100 million study will run for five years, but results on sophisticated tests may indicate in as little as two years whether the drug is helping to delay memory decline or brain changes, said Dr. Eric M. Reiman, executive director of the Banner Alzheimer's Institute in Phoenix, and a lead researcher on the study.

Dr. Reiman and Alzheimer's experts not involved in the study say that though a relatively small percentage of people with Alzheimer's have the genetic early-onset form that affects the Colombian family, the trial is expected to answer questions that could apply to the millions of people worldwide who will develop more conventional Alzheimer's disease.

"It offers a tremendous opportunity for us to answer a large number of questions, while at the same time offering these people some significant clinical help that otherwise they never would have had," said Dr. Steven DeKosky, an Alzheimer's researcher who is vice president and dean of the University of Virginia School of Medicine. Dr. DeKosky was part of a large group of experts

consulted in early discussions about a prevention trial, but is not involved in the study.

Some 5.4 million Americans currently have Alzheimer's disease, and the numbers are expected to swell as the baby boom generation ages. Dr. Reiman and his team are already planning a similar drug trial for people considered to be at increased risk for conventional Alzheimer's in the United States. The study announced Tuesday will include a small number of Americans with gene mutations guaranteed to cause early-onset Alzheimer's. The study is part of the federal government's first national plan to address Alzheimer's disease, details of which were unveiled Tuesday by Kathleen Sebelius, the secretary for health and human services. In it, the government took the unusual step of finding $50 million from the current year's N.I.H. budget to pay for research including the Colombia trial. An additional budget increase of $100 million is proposed for 2013, mostly for research, but some of it for education, caregiver support and data collection.

Whether the Colombia trial will succeed is, of course, no sure thing. Many clinical trials fail, and the history of Alzheimer's research is marked by a frustrating results from treatments it was hoped would be promising. But the unique nature of trying a drug years before a person's brain is ravaged by the disease is considered a promising approach to identifying what causes Alzheimer's and how to potentially prevent the disease. The Colombia drug trial will be financed with $16 million from the National Institutes of Health, about $15 million from private donors through the Banner Institute and $65 million from Genentech, the drug's American manufacturer.

If the drug, Crenezumab, which attacks the formation of amyloid plaques in the brain, is shown to forestall memory or cognitive problems, plaque formation or other signs of brain deterioration, scientists will have discovered that prevention or delay is possible and that the answer would appear to lie in targeting amyloid years before dementia develops. Many, but not all, Alzheimer's researchers believe that amyloid is an underlying cause of Alzheimer's.

"We really believe in wanting to help these folks, and if in fact we can really prevent the disease, it holds tremendous potential for preventing the disease in a broader population," said Richard Scheller, Genentech's executive vice president of research and early development.

In 2010, The New York Times reported on the tragedy of dementia in this large Colombian family. Many of the relatives are debilitated in their prime working years as their memories unravel, and the disease eventually assaults their ability to move, eat, speak and communicate. At the time, a team of scientists in Colombia and Arizona were laying the groundwork for a study to test medications on family members.

Dr. Reiman said his team worked to persuade pharmaceutical companies to invest in the unusual, and sensitive, research. "We would have to be like Mark Twain," he said, "getting the companies to pay to whitewash the fence and give us access to their most promising treatments."

But it took months of painstaking planning to navigate the thorny scientific and ethical issues involved in giving drugs to people who are healthy.

“There’s a lot at stake here,” said Dr. Pierre N. Tariot, director of the Banner Alzheimer’s Institute and a leader of the study. “We have to do everything we can to do it in the right way.”

Researchers, American officials and drug companies were especially sensitive to the fact that the study would be conducted on people in a developing country, many of whom have little education, paltry incomes and a history of superstitions about the disease they call “la bobera” — the foolishness.

“The first thing I did was to ask myself the question, are we taking advantage of these folks?” Dr. Scheller said. “The answer was clearly no.”

The risks, he said, were balanced by the fact that if nothing is done, “they’re going to get this terrible, terrible disease for sure.”

Finding a way to prevent or delay Alzheimer’s is a priority for scientists because decades of research have resulted in only a few drugs that can treat dementia once it starts, and that delay decline for only a few months. In addition, researchers have learned that the brain begins deteriorating as long as 20 years before dementia begins. Many scientists believe that waiting until symptoms appear is much too late to begin treatment because the brain has already been so significantly damaged.

Prevention studies have been difficult and expensive to do, primarily because the cause of most Alzheimer’s is unclear and it is impossible to predict exactly who will develop it. The few trials of prevention therapies — involving ginkgo biloba, women’s hormone replacement treatment, and anti-inflammatory drugs — have involved people not guaranteed to get the disease. These therapies either failed or caused adverse side effects.

Testing drugs on that kind of population “would take too many healthy volunteers, too much money, and too many years to wait for enough people to develop memory and thinking problems to see if treatment worked,” Dr. Reiman said. The Colombian population is ideal for such tests because it is large enough to provide solid results, and it is easy to identify whom the disease will strike, and when.

Crenezumab, the drug in the Colombia trial, was chosen in part because it appears to be safer than other drugs that are designed to clear amyloid from the brain, said Dr. Francisco Lopera, a Colombian neurologist who is a leader of the study. Other anti-amyloid treatments have caused edema in the blood vessels, an imbalance of fluid that can cause serious side effects.

In safety studies on Crenezumab, “people didn’t have that problem,” said Dr. Lopera, who has worked with the Colombian family for decades and, with Dr. Kenneth S. Kosik of the University of California, Santa Barbara, identified the family’s illness as Alzheimer’s and the genetic mutation that causes it.

Crenezumab is currently being given in two clinical trials to people with mild to moderate symptoms of dementia in the United States, Canada and Western Europe to see if it can help reduce cognitive decline or amyloid accumulation, according to Genentech.

In the Colombia study, expected to start early next year, 100 family members who carry the mutation will receive the drug every two weeks in an injection administered at a hospital. Another 100 mutation carriers will receive a placebo. And because many people do not want to know if they have the mutation, researchers will also include 100 non-carriers in the study; they will receive a placebo.

“I can’t think of a trial that’s been done like this,” Dr. Scheller said. In other trials, including those involving people with dementia, “they know they have it.”

Many tests will be used to evaluate whether the drug is effective. Researchers have developed a sophisticated battery of five memory and cognitive tests that have been shown in other studies to detect subtle alterations in recall and thinking ability that usually go unnoticed.

The measurements, Dr. Tariot said, will involve recalling a list of words after a period of distraction, naming common objects, a nonverbal reasoning test, answering questions about time and place, and a drawing test in which participants copy increasingly complex figures.

“The question is, does the treatment slow down loss of memory in carriers?” Dr. Tariot said. “Does it slow down the likelihood of developing typical aspects of dementia like mild cognitive impairment?”

Dr. Tariot said researchers will also assess changes in people’s emotional state, “irritability, sadness, crying, anxiety, impulsivity — these are cardinal features of the disease as it emerges.”

The scientists will also take physiological measurements, including PET scans that measure amyloid, PET scans that measure how glucose is metabolized in the brain, M.R.I. scans that measure whether the brain is shrinking, and cerebral spinal fluid tests that measure levels of amyloid and tau, a protein that accumulates in dying brain cells.

If any of these biochemical indicators or biomarkers ends up being improved by the drug, that could be another important scientific breakthrough, Dr. Reiman said. Scientists might then be able to treat one of these Alzheimer’s biomarkers, in the same way that high blood pressure and

cholesterol are considered treatable biomarkers of impending heart disease.

For Dr. Lopera, the approval of the study is not only a scientific milestone, but a hard-won personal victory after years of observing the agony of so many family members.

“This is an opportunity that they were waiting for a long time,” Dr. Lopera said. “This is the first time that we can give them hope.”

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