Medical News & Perspectives

Much Anticipated Alzheimer Disease Prevention Trial Finds No Clinical Benefit From Drug Targeting Amyloid; Highlights Need to Consider Other Approaches

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The Paisa mutation, nicknamed for the people of northwest Colombia’s Antioquia region in whom it is found, is associated with sticky clumps of protein in the brain called amyloid-β plaques, one of the hallmarks of Alzheimer disease.

Individuals who inherit a copy of the Paisa mutation—E280A in the presenilin 1 gene—from one of their parents develop mild cognitive impairment by 44 years of age, on average, and Alzheimer disease 5 years after that. Typically, they die within a few years after their 59th birthday.

Researchers in the US and Colombia have identified about 1200 members of an extended family of 6000 people, most of them living in and around Medellín, Colombia, who carry the Paisa mutation, the most common cause of familial, early-onset Alzheimer disease.

“A rare but tragic family,” probably descendants of a conquistador who lived centuries ago, is how Richard Hodes, MD, director of the National Institute on Aging (NIA), described them in an interview with JAMA.

Between the prevalence of autosomal dominant Alzheimer disease (ADAD) in the Paisa region and its inhabitants’ history of a high level of participation in Alzheimer disease research, “this seemed to be an enormously powerful place to test the hypothesis,” Hodes said.

“The hypothesis” Hodes was referring to is what has come to be known as the “amyloid cascade hypothesis,” an idea born 30 years ago when 2 UK scientists proposed that amyloid-β deposition in the brain—first described by German psychiatrist and neuropathologist Alois Alzheimer in 1906—was “the central event in the etiology of Alzheimer’s disease.”

According to the hypothesis, reducing amyloid-β plaque in the brain should prevent or slow the progression of Alzheimer disease, and that has led to clinical trials of one antiamyloid therapy after another in the search for an effective treatment.

Whether amyloid-β deposits cause Alzheimer disease still isn’t clear. Although higher levels of plaques—detected via positron emission tomographic (PET) scans or cerebrospinal fluid or on autopsy—are associated with more advanced Alzheimer disease, some people with amyloid plaques in the brain never experience cognitive impairment.

Disappointing Results

In 2012, the National Institutes of Health (NIH) announced a landmark $100 million project, the first-ever Alzheimer disease prevention trial, that would test an antiamyloid monoclonal antibody called crenezumab in members of the Colombian extended family. The trial, part of the international Alzheimer’s Prevention Initiative, would go on to enroll 252 people between the ages of 30 and 60 years who had no Alzheimer symptoms at baseline.

However, a decade after the trial was announced, in June of this year, the NIA and trial collaborators the Banner Alzheimer Institute and Genentech issued press releases announcing disappointing news: compared with placebo, crenezumab did not demonstrate a statistically significant clinical benefit in people with the Paisa mutation after 5 to 8 years of treatment.
Focusing on a family in which every member has a high risk of developing early-onset Alzheimer disease served as a shortcut for a prevention trial, Eric Reiman, MD, one of the lead investigators, told JAMA. Trying to answer the same question in the general population, most of whom are destined to never develop Alzheimer disease, would be cost- and time-prohibitive because it would require studying approximately 50,000 participants for 25 years, he said.

Two-thirds of the participants in Reiman’s trial carried the Paisa mutation, and they were randomized to receive infusions of crenezumab or a placebo. Participants who weren’t carriers of the mutation received only the placebo. (Although all participants underwent genetic testing, they weren’t told whether they carried the mutation; noncarriers received placebo infusions instead of nothing at all so as not to reveal who carried the Paisa mutation and who didn’t.)

One reason crenezumab was selected for the trial was because it didn’t provoke amyloid-related imaging abnormalities (ARIA), which are swelling or bleeding in the brain that can lead to confusion, altered mental status, and disorientation. ARIAs, seen with other antiamyloid monoclonal antibodies, usually resolve over time. Because crenezumab wasn’t associated with ARIAs and appeared to have a low rate of other adverse effects, the Colombia trial started the treatment group on a dose higher than used in previous trials of other antiamyloid monoclonal antibodies and increased it 7-fold over the course of the study.

Although the differences between the treatment and placebo groups weren’t statistically significant, “[i]t is striking that all the clinical and most of the biomarker data favor active treatment, though confidence intervals are broad,” dementia specialist Gil Rabinovici, MD, said in an interview with JAMA. Rabinovici, who wasn’t involved with the Colombia study, is director of the University of California, San Francisco, Alzheimers Disease Research Center and an associate editor of JAMA Neurology.

Reiman, executive director of the Banner Alzheimer Institute in Phoenix, and several of his collaborators reported their results August 2 at the Alzheimer’s Association International Conference in San Diego.

“When we designed the trial, we assumed a 5% dropout per year,” Pierre Tariot, MD, director of the Banner Alzheimer Institute, said at the conference. Instead, only 4% of participants in total dropped out, “an extraordinary testimony” to the families and the research team at the University of Antioquia, Tariot said at the conference.

Hindsight
Reiman has several theories about why crenezumab didn’t demonstrate a statistically significant clinical benefit in the Colombia trial.

Trial participants who were carriers were several years younger and approximately half as likely to have amyloid deposits at the beginning of the trial as the researchers had expected based on observational data from the kindred, Reiman said.

Their average age was 37 years, instead of 41 years, and 45% had no amyloid deposits at baseline, although the researchers had expected only a quarter of them would have no deposits, he said. As a result, Reiman explained, there was less progression in the placebo group than anticipated, contributing to reduced power to detect significant slowing in the treatment group.

Also, he speculated, participants might have been receiving too low a dose of crenezumab for most of the trial. They received the highest dose for only 2 years, he pointed out.

“We cannot tell you with certainty whether a higher dose might have had a clinical benefit,” Reiman said during the panel discussion about the trial at the Alzheimer’s Association conference.

Unlike other monoclonal antibodies directed at different targets in the amyloid pathological pathway, crenezumab didn’t slow the deposition of plaque, Reiman said. Although he and his collaborators didn’t anticipate a dramatic impact on plaque, “we had expected we might see a slowing of the increase,” he said at the conference.

All study participants with the Paisa mutation are now receiving crenezumab, while those who don’t carry a copy of the mutation are continuing to receive infusions of the placebo—again, so no one learns their carrier status.

Trial data are still being analyzed, Reiman said at the conference. “We think these data will be invaluable in planning future trials.”

Déjà Vu All Over Again?
The Colombia trial was just the latest in a series of trials of crenezumab and other anti-amyloid therapies that have failed to show a clinical benefit.

A recent review article in the Journal of Alzheimer Disease identified 9 compounds targeting amyloid that had failed in phase 3 trials since 2018.

In January 2019, Roche, Genentech’s parent company, announced it was discontinuing 2 phase 3 trials of crenezumab in patients with mild, sporadic Alzheimer disease because preplanned interim analyses concluded that the treatment was unlikely to meet its primary endpoint of slowing cognitive decline.

And a year before the findings of the Colombia crenezumab trial were reported, the US Food and Drug Administration (FDA) approved aducanumab (Aduhelm), another antiamyloid monoclonal antibody, even though none of the agency’s panel of outside experts had voted “yes” when asked whether clinical trials had shown it to be effective in treating Alzheimer disease.

The agency granted aducanumab “accelerated approval,” which is based on a surrogate end point—in this case, a reduction in amyloid-beta plaque in the brain—that, according to the FDA, “is reasonably likely to predict a clinical benefit to patients.” Aducanumab, the only antiamyloid drug that has ever received FDA approval, is the first Alzheimer therapy designed to modify the underlying disease process and not just treat symptoms.

After the FDA approved aducanumab, the Centers for Medicare & Medicaid Services (CMS) released a national coverage policy for the therapy as well as future anti-amyloid antibodies to spur the collection of more information about their safety and effectiveness.

Medicare will cover aducanumab and other such therapies granted accelerated approval based on a surrogate end point, such as amyloid reduction, only for beneficiaries participating in FDA-sanctioned randomized clinical trials to determine clinical effectiveness. Aducanumab isn’t cheap. In January, Biogen cut the drug’s wholesale acquisition cost in half, to $28,200 per year for an average-size patient (dosing is based on patients’ weight).

For monoclonal antibodies that receive FDA approval via the conventional
pathway, which involves demonstrating clinical benefit, Medicare will still only cover the cost for patients in CMS-approved or NIH-supported studies.

**Time to Move on From Amyloid?**

Although Reiman says the study in Colombia neither confirms nor refutes the amyloid hypothesis, one might wonder whether crenezumab's and other amyloid treatments' failures to show a clinical benefit in multiple trials sounds the death knell for the theory.

“All these antibodies are different,” Allan Levey, MD, PhD, director of Emory University’s Goizueta Alzheimer Disease Research Center, told JAMA. “Maybe [crenezumab] is just the wrong antibody, but man, it’s a downer that it didn’t work” to prevent Alzheimer disease in the Colombia trial.

The amyloid hypothesis “is a well-accepted hypothesis,” Matthew Schrag, MD, PhD, assistant professor of neurology at Vanderbilt University School of Medicine, said in an interview with JAMA. “The main problem with it is it’s not working in clinical trials.”

Schrag recently raised concerns that a number of research articles about an amyloid-β oligomer dubbed Aβ*56 might include manipulated or misrepresented images, and many of the papers, published in leading journals such as Nature and Science, have now been retracted or labeled with expressions of concern by editors.

No experimental therapy based on Aβ*56 has ever been developed, Hodes noted in a July 29 statement. While Aβ*56 “caused some initial interest, it resulted in a limited line of subsequent research because of the lack of specific markers to detect it in laboratories and the inability to reproduce the initial findings,” he said. “Despite the data from some recent clinical trials on amyloid-directed antibodies, there is still a strong scientific rationale for continuing to explore approaches that target different aspects and collections of the amyloid protein.”

One possible reason that clinical trials of anti-amyloid therapies for Alzheimer disease failed, the recent Journal of Alzheimer Disease review article pointed out, is that some trial participants may have been misdiagnosed and didn’t actually have Alzheimer disease, which is the most common cause of dementia. (The authors noted that misdiagnosis is less likely today thanks to advancements such as the use of amyloid-β and other biomarkers.)

Like Levey and Schrag, Sam Gandy, MD, PhD, director of the Mount Sinai Center for Cognitive Health in New York, has criticized the FDA’s approval of aducanumab because evidence of clinical benefit is lacking. “There is no consistent relationship between amyloid fibril [strands] burden and cognition, and it seems to me that it is time to move on beyond this simplistic formulation,” Gandy told JAMA recently.

Not so fast, Rabinovici said. Within the next year, clinical trial results for 3 other anti-amyloid-β monoclonal antibodies should finally settle the question of whether amyloid is a useful target for Alzheimer disease therapies, he explained.

The 3 are Eli Lilly’s donanemab, Eisai’s lecanemab, and Roche and Genentech’s gantenerumab. Reiman is one of the lead principal investigators for a donanemab phase 3 prevention trial involving individuals 55 years to 80 years of age who are at risk of Alzheimer disease based on elevated plasma levels of plasma phospho-tau217 (P-tau217), a promising biomarker.

A recent meta-analysis of data from trials of donanemab, lecanemab, gantenerumab, and aducanumab found that the extent of amyloid removal among the 4 therapies varies. Higher amounts of amyloid removal were correlated with a better clinical response in patients with early Alzheimer disease, according to the meta-analysis. However, the authors noted that higher levels of amyloid removal were also associated with a greater risk of ARIA, suggesting, they said, that the balance between amyloid removal and risk of ARIA is relevant for deciding what dose to use in clinical trials.

Based on early-stage trials, the FDA has designated all 3 of the experimental monoclonal antibodies as “breakthrough therapies,” a category “designed to expedite the development and review of drugs that are intended to treat a serious condition,” according to the agency. The FDA designates treatments as breakthroughs because preliminary clinical evidence “indicates that the drug may demonstrate substantial improvement over available therapy on a clinically significant endpoint(s).” Generally, such end points measure an effect “on irreversible morbidity or mortality...or on symptoms that represent serious consequences of the disease.”

However, as other therapies targeting amyloid have shown, preliminary clinical evidence of efficacy in early-phase trials doesn’t always pan out in larger phase 3 trials.

**Branching Out**

No matter their opinion about the usefulness of targeting amyloid, dementia experts seem to agree that the complexity of Alzheimer disease calls for a multipronged treatment approach tailored to the particular patient, depending on such factors as the stage of their disease.

“I have a hard time imagining how targeting any single molecule or any single pathology is likely to yield a meaningful clinical benefit,” Gandy said.

Although the final answer on amyloid may not yet be in, researchers are branching out in their search for tools—both drugs and lifestyle changes—that could at least slow the development or progression of Alzheimer disease.

“A decade ago, there wasn’t much in terms of alternative targets” to amyloid, Hodes said. To illustrate his point, he noted that 5 of the 8 late-stage Alzheimer trials funded by the NIA involve anti-amyloid therapies. However, Hodes said, only 13 of the 61 phase 1 or phase 2 trials receiving NIA funding target amyloid.

Nonamyloid therapeutic targets include other proteins, such as tau—tau neurofibrillary tangles are a hallmark of Alzheimer disease that haven’t received as much attention as amyloid plaques—TDP-43 (transactive response DNA-binding protein 43), the accumulation of which in the central nervous system is also a feature of other neurodegenerative diseases; and α-synuclein, which appears to interact with tau in neurodegenerative diseases, Hodes said. Besides proteins, other Alzheimer therapeutic targets for which the NIA is funding trials include inflammation, genetics, and vascular system changes, he said.

The NIA is also supporting 131 studies of nonpharmacological interventions focused on cognitive training, sleep, and exercise, among others, Hodes said. One NIA-funded phase 3 trial presented at the Alzheimer’s Association conference evaluated whether regular exercise could...
benefit people with amnesic mild cognitive impairment (MCI), which primarily affects memory and increases the risk of Alzheimer disease or related dementias.

The trial randomized 296 adults to either moderate-intensity aerobic training or low-intensity stretching, balance, and range-of-motion exercises for 18 months. Exercise sessions took place at a YMCA 4 times a week for a total of 120 minutes to 150 minutes per week. In the first 12 months, a trainer supervised 2 sessions a week, while the other 2 were unsupervised. All exercise was unsupervised in the last 6 months. Neither group showed significant declines from baseline in the primary measure of cognitive function over 12 months, suggesting that both the moderate- and low-intensity exercise, and, possibly, the socialization participants received with it, stalled cognitive decline, researchers reported at the meeting. In contrast, cognitive function did decline over a year in similar adults with MCI who participated in a large “usual care” observational study.

Approximately 6.5 million people aged 65 years or older in the US are living with Alzheimer disease, and that number is expected to nearly double by 2050, according to the Alzheimer’s Association.

“The stakes are too high just to focus on amyloid,” Reiman said.

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