Amyloid Theory of Alzheimer's Not Dead—Yet

BY MICHELE G. SULLIVAN
Mid-Atlantic Bureau

The amyloid hypothesis is not dead, but it seems to be limping a bit in the race for an Alzheimer's cure.

Some researchers who predicted 5 years ago that an anti-amyloid disease-modifying therapy was imminent are now re-evaluating that optimism—including the geneticist who first suggested the pathologic link between amyloid plaque deposition and Alzheimer's disease.

"I accept that criticism of myself; it's definitely what I thought," John Hardy, Ph.D., said in an interview. "Everything is taking a lot longer than I thought it would, there's no question about that."

In 1991, Dr. Hardy, a professor of neuroscience at University College London, postulated that β-amyloid deposition was the root of a pathologic cascade that resulted in Alzheimer's disease. The concurrent discovery that a mutation in the amyloid precursor protein (APP) gene caused early-onset Alzheimer's, coupled with the association of plaque deposition and early Alzheimer's in Down syndrome patients, added weight to the theory (Trends Pharmicol. Sci. 1991;12:383-8). A new research boom was born.

The protein was a near-ideal therapeutic target because there are many ways to get at it: immunotherapy to break up existing plaques, compounds to prevent formation of the sticky β-amyloid-42, and antiaggregants to prevent the protein from clumping into neurotoxic plaques. But the first phase III trials of antiamyloid have brought no good news.

Tramiprosate, a β-amyloid antagonist, was the disappointment of 2007; tarenflurbil, a gamma-secretase modulator, this year's downer. And although bapineuzumab, a passive immunotherapy, made it to phase II last summer, positive findings in its phase II trial were slim. A post hoc analysis showed that some patients with mild-moderate Alzheimer's, with no genetic risk factors, had cognitive improvement after getting the vaccine.

Apparently, the finding was enough for Elan Pharmaceuticals Inc., and Wyeth Pharmaceuticals, but maybe not for Dr. Hardy. "The data right now are neither positive nor negative. At this point, the only thing we can say about bapineuzumab is that it's not going to be a miracle therapy," he said.

A long-term follow-up study of patients enrolled in the early AN-1792 immunotherapy trial "doesn't look great for amyloid, either," he said. The AN-1792 trial was halted early, in 2002, when some of the patients developed encephalitis after getting the vaccine. The follow-up, published last summer, showed that the vaccine did clear plaques, but that clearance did not affect cognition or survival (Lancet 2008;372:216-23).

Dr. Hardy doesn't think that slow progress on antiamyloid drugs negates the theory's basic truth, though—at least for a subset of patients. "A much more open debate is whether the same process is at work in the typical Alzheimer's patient."

But drug companies must target this larger population to create a financially successful therapy, and lack of progress has them fidgeting, he said. "Every drug company is worried now and wondering if they should widen to other therapies, including tau-targeted drugs."

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Dr. Rachelle Doody says the phase II trial of bapineuzumab "at least had some signal" that the agent is safe and effective.

The essential mystery of amyloid further complicates things, Dr. Hardy said: The protein has not yielded up all its secrets, despite years of research. "The thing that keeps me up at night is that we don't really know if amyloid has a function. It could be that amyloid is a response to vascular damage. We all ignore the fact that amyloid deposition occurs to a large extent in the vasculature. There must be a reason for this."

That worry also plagues Mark A. Smith, Ph.D., professor of pathology and an Alzheimer's researcher at Case Western Reserve University, Cleveland. "We have said for a long time that amyloid is doing something important in the brain. It could be acting like a vascular sealant in areas of injury. It forms structural scaffolding for blood vessels, and if you start getting rid of that scaffold, you'll see problems in the blood-brain barrier." This reaction probably caused the brain inflammation seen in the AN-1792 trial, he said.

Dr. Smith, a paid consultant for several companies investigating non-amyloid–related therapies, is among a minority of researchers who resist the amyloid theory. The amyloid research momentum, he said, is so strong right now that only more high-profile failures will begin to temper it."People still can't believe it's not working, and they're waiting for the results of the phase III vaccine trial," as well as new data on β-secretase inhibitors, theorized to reduce the buildup of plaque-forming AB-42, he said.

Dr. Rachelle Doody, director of the Alzheimer's Disease and Memory Disorders Center at Baylor College of Medicine, Houston, thinks that the failure of antiamyloid drugs illustrates not a failure of the theory, but the failure of specific drugs and possibly the failure of drug companies to follow a comprehensive and logical phase II plan.

"Companies want their drug to be labeled as a disease-modifying agent as soon as possible," she said in an interview. And because they are going for that, they are designing phase II trials that are long and costly but don't give them all the information they need."

Ideally, when any agent finishes phase II, there should be clear evidence that it is safe and effective in the primary end point. "Neither tramiprosate nor tarenflurbil had a clear signal in phase II, and neither did bapineuzumab, although it at least had some signal," she said.

Companies could also modify their research track to prove first that a drug confers symptomatic benefit, and then examine its possible disease-modifying properties. That is the path Medivation Inc. is following with dimebon—the only bright note in late-stage clinical trials this year. The obscure Russian antihistamine, thought to boost mitochondrial function, succeeded where the anti-amyloids failed, significantly improving cognition, behavior, and function in Alzheimer's patients, although it did not modify disease progression.

"Dimebon probably is a disease-modifying drug, but proving this requires long-term studies," said Dr. Doody, primary investigator on the phase II trial. "But many pharmaceutical companies fear that a drug will be priced too low if they go for symptomatic approval first without the disease-modifying work up front."

Dr. Marwan Sabbagh, chief medical and scientific officer of Sun Health Research Institute, Sun City, Ariz., suspects that researchers might be looking at antiamyloids through the wrong end of the lens. Rather than a one-step cure, the compounds may be best used in primary prevention. "The problem is, we may be approaching it too late," he said in an interview. "By the time you clinically manifest dementia, it might be too late for the drugs to help, even if they clear the plaques." ■

Methylphenidate Reduces Alzheimer's Apathy, Caregiver Distress

BY MICHELE G. SULLIVAN
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CHICAGO — Methylphenidate appears to improve the symptoms of apathy in patients with early Alzheimer's, benefiting both patients and caregivers, according to a small prospective trial.

After taking the drug for 12 weeks, patients showed significantly reduced frequency and severity of apathy, while their caregivers reported significantly reduced distress, Dr. Prasad Padala said at the International Conference on Alzheimer's Disease.

"Apathy is the most common behavioral and psychiatric symptom of dementia, occurring in up to 90% of patients, and it's one of the earliest symptoms to appear," said Dr. Padala of the University of Nebraska Medical Center, Omaha.

"Apathy also causes the caregivers a lot of stress, and it has a very high impact on functional status. Patients with apathy are three times more likely to be dependent on caregivers for their activities of daily living than are patients without apathy."

It's thought that dysregulation of both the dopaminergic and noradrenergic systems contribute to apathy, and methylphenidate works on both of these systems.

The study enrolled 20 patients (mean age 70 years) at the Veterans Affairs Medical Center, Omaha. All had early Alzheimer's disease, with a mean Mini-Mental State Examination score of 23 and a score above 30 on the Apathy Evaluation Scale, indicating significant apathy.

At baseline, patients were assessed with the Neuropsychiatric Inventory's apathy subscale. This system scores apathy on a 1- to 4-point scale for frequency and on a 1- to 3-point scale for severity. The score is a product of the two ratings. Caregivers rate their distress on a 1-5 scale, with 5 being the greatest.

Patients were started on 5 mg methylphenidate twice daily, and titrated up to 10 mg twice daily. Follow-up visits were conducted at 4, 8, and 12 weeks. After 12 weeks of treatment, patients significantly improved in their total item score from baseline (5 vs. 1.6), as well as their frequency/severity score (9 vs. 2). Caregiver distress also improved significantly, decreasing from 3.25 to 1.

"Caregivers noted substantial improvements in the patients, such as increased energy, spontaneity, motivation, and ambition," Dr. Padala said at the meeting, sponsored by the Alzheimer's Association.

Two patients needed reductions in methylphenidate dosing: one for loss of appetite and the other because of a blood pressure increase, said Dr. Padala, who had no financial disclosures with regard to the study drug. ■