Early Use Is Key

Antiamyloids *from page 1*

produced when the enzymes β- and γ-secretase cut the amyloid precursor protein into different lengths. Inhibitors of γ-secretase stop that cleavage, lowering Aβ levels by keeping the precursor protein intact. Selective amyloid-lowering agents (SALAs) also work on γ-secretase: They change the point where the protein is cut, preventing the formation of the toxic, longer-chain Aβ-42. Both γ-secretase inhibitors and SALAs are designed to reduce soluble Aβ levels, with the aim of preventing plaque formation.

The third agent under development—an Aβ antagonist—is designed to maintain Aβ peptides in a soluble state. It apparently stops heparin from binding to Aβ, an interaction thought to trigger Aβ aggregation, said Dr. Wolfe. This compound, which is furthest along the developmental pipeline, not only reduces soluble Aβ, but has been shown in animal models to reduce the load of already-formed Aβ-42 plaques.

Safety and Efficacy

Some serious safety issues plagued the γ-secretase inhibitors during early preclinical development, Dr. Wolfe said. The enzyme also plays a key role in cell signaling from the Notch receptor: Blocking it entirely had significant effects on this pathway, which mediates cell differentiation and proliferation. Immune cells and tissues with high cellular turnover—including gut tissue—were most severely affected.

The SALAs don't block γ-secretase, but rather modify the enzyme's activity in a way that avoids the Notch problem. But, Dr. Wolfe said, early SALAs just weren't very effective in cell cultures. "Even the one in clinical trials requires very high doses," to achieve a significant effect. "They're apparently very safe, however," he added.

The Aβ antagonists have likewise shown little or no toxicity in humans, even at very high doses, he said.

Tramiprosate: Aβ Antagonist

Of all the Aβ modulators, tramiprosate (Alzhemed, Neurochem Inc.) is closest to clinical use. Its initial 18-month phase III trial, which includes 1,052 North American patients with mild to moderate Alzheimer's, is set to conclude in January 2007; a similarly sized European trial is underway.

Findings from in vitro experiments have shown that the drug inhibited Aβ-42–induced cell death by 38%. In animal studies, it reduced Aβ-42 plasma levels by 31% and plaque burden by 24% (Neurobiol. Aging 2006, May 1;[Epub ahead of print]doi:10.1016/j.neurobiolaging.2006.02.015).

The findings of a phase II study of 58 patients with mild to moderate Alzheimer's, who were followed for almost 3 years, are consistent with those early results. Over the first 3 months of that trial, patients on the highest dose of tramiprosate had a significant decrease in mean levels of Aβ-42 in cerebrospinal fluid compared with placebo patients. "The reductions varied depending on the dose given, but the average decrease was up to 30%, which reproduced quite nicely what we saw in the animal studies," said Denis Garceau, Ph.D., Neurochem's senior vice president of drug development.

Tramiprosate also has some ability to stabilize disease progression and perhaps even modify its course, he said. After 20 months on the drug, about 70% of the patients with mild Alzheimer's who were still receiving tramiprosate showed either stabilized or slightly improved cognitive measures.

There were no significant adverse effects; the most frequent were mild to moderate gastrointestinal symptoms that resolved spontaneously.

Both phase III trials are testing two, twice daily doses (100 mg and 150 mg) against placebo, and will be followed by an 18-month open-label extension. About 350 patients have already completed the North American trial, and 85% of them have signed onto the extension study.

Some of the phase III study patients will have pre- and posttherapy MRI to help evaluate the drug's effect on brain atrophy.

R-flurbiprofen: SALA

Myriad Genetics Inc. is just revving up its phase III trials for this drug (Flurizan). The U.S. trial is in its last stage of recruitment, looking for 1,600 Alzheimer's patients with mild disease. A global study will enroll 800 patients. Both are 18-month trials that pit R-flurbiprofen (800 mg twice a day) against placebo.

The earlier in the course of disease patients take R-flurbiprofen, the bigger the cognitive benefit, with some people with mild disease gaining ground.

R-flurbiprofen rode an efficacy seesaw during its phase II trials. Preliminary results showed no significant effects in any of the three end points (activities of daily living, dementia score, and cognitive function) for the overall group of 207 patients with mild to moderate disease. However, patients with mild AD who were taking the 1,600-mg/day dosage showed a statistically significant benefit at 12 months in activities of daily living and global function, with a positive trend in the Alzheimer's Disease Assessment Scale with the cognitive function subscale (ADAS-cog) (Neurology 2006;66 [Suppl 2]: A347).

The 12-month follow-up study showed that patients with mild disease who stayed on the drug continued to improve, actually regaining up to 2 points on the ADAS-cog. "Although not statistically significant, we saw that the less advanced the patients' disease, the bigger the response they get from the drug," said Adrian Hobden, Ph.D., president of Myriad.

An additional benefit of R-flurbiprofen may be its ability to delay the onset of psychiatric symptoms in Alzheimer's patients, according to data presented in a poster at the 10th International Conference on Alzheimer's Disease and Related Disorders, held in Madrid. In a secondary analysis of the phase II trial, Dr. Jacobo Mintzer, of the Medical University of South Carolina in Charleston, showed that by 1 year, about 90% of patients on the 1,600-mg/day dosage were free of psychiatric symptoms, compared with about 70% of those on placebo.

The European trial will collect cerebrospinal fluid at baseline and at 18 months for exploratory biomarker studies, once reliable markers have been identified.

Myriad is contemplating separate imaging studies to examine hippocampal and whole-brain volume changes associated with the drug. An exploration of the drug's effect on amyloid plaque deposition with PET imaging using Pittsburgh Compound B is also a possibility. Such studies may be key to demonstrating whether the drug has any effect on existing brain plaques in humans. In a mouse model, it reduced plaque load and was associated with improved spatial learning and memory.

LY450139: γ-Secretase Inhibitor

Eli Lilly & Co. will get its first glimpse of this drug's effect in cognitive and functional domains from a 29-week phase IIB study, launched at six U.S. sites earlier in 2006. The trial will include 45 patients with mild to moderate Alzheimer's randomized to placebo or LY450139.

Two previous human trials demonstrated the compound's ability to significantly lower total Aβ levels in plasma, but were unable to show a significant decrease in cerebrospinal fluid levels.

Both studies provoked concern among the research community for adverse events that could be tied to Notch signaling toxicity. In the 2004 dose-ranging trial (Clin. Neuropharmacol. 2005;28:126-32), two of seven healthy volunteers who took the 50-mg/day dosage for 2 weeks withdrew: one for an increase in serum amylase and lipase concentrations and exacerbation of previous gallbladder and biliary disease, and the other for nausea, vomiting, weakness, and diarrhea accompanied by elevation in white blood cell count.

A single death occurred during the 2005 trial (Neurology 2006;66:602-4). In this study, 70 patients with mild to moderate Alzheimer's took placebo or a titrated lower dose of the drug (1 week of drug at 30 mg/day followed by 5 weeks at 40 mg/day). One patient in the active group died from endocarditis 5 months after withdrawing from the trial as a result of gastrointestinal bleeding from Barrett's esophagus. Neither the endocarditis nor the Barrett's was associated with the drug, according to the study: The esophageal histology didn't show goblet cell hyperplasia, a characteristic sign of Notch signaling interrupted by a γ-secretase inhibitor.

Other patients may have shown mild Notch toxicity. Diarrhea was more common among the active group (six subjects vs. none taking placebo), but reports of "loose stool" were more common among placebo-treated subjects (in one subject vs. six taking placebo). Active patients also had small but significant increases in T lymphocyte and eosinophil counts.

The short half-life of LY450139—only 2.5 hours—may be its saving grace in this area, Dr. Eric Siemers, medical advisor for Lilly, said in an interview. "Based on our data thus far, in adults you can apparently inhibit Notch signaling for up to 12 hours a day and not really see any Notch-related toxicity."

The Future

The biggest bang of LY450139 and similar compounds will probably be in their ability to forestall cognitive decline, Dr. Siemers said. He and other researchers envision a time when advances in imaging and biomarkers will foster the advent of a regular dementia screen as people approach old age—something akin to today's colorectal-screening process.

Those who screen positive—perhaps by a brain imaging study showing amyloid plaque deposition—will immediately receive a disease-modifying drug, or perhaps a cocktail of remedies including Aβ-modulators and immunotherapy. "These things could be used presymptomatically to catch people before they experience significant decline," Dr. Siemers said.

Drug research will combine in a very powerful way with advances in markers and imaging technology to improve social acceptance of early diagnosis, predicted Dr. Paul Aisen, of Georgetown University Medical Center in Washington. "Today, there is nothing you can do for these patients," said Dr. Aisen, Neurochem's principal U.S. investigator of tramiprosate. "At diagnosis, you are basically giving them a death sentence, so right now there is a great deal of reluctance to diagnose someone early.

"But if you have a way to detect early changes, and drugs that will prevent progression, that will change our entire outlook on early diagnosis, and that's what we need. We need to change society's perception of this from something that kills you to something you can live with." ■

Subclinical Cognitive Decline Emerges Early in Apo E4 Carriers

MADRID — Asymptomatic carriers of the apo E4 gene show significant longitudinal decline on measures of frontally mediated cognitive skills and memory, Dr. Richard Caselli reported at the 10th International Conference for Alzheimer's Disease and Related Disorders.

Dr. Caselli, chairman of neurology at the Mayo Clinic, Scottsdale, Ariz., followed 35 apo E4 carriers and 33 noncarriers for at least 6 years, during which time all study participants received neuropsychological testing every other year.

Patients who developed symptomatic cognitive impairment were dropped. At baseline, carriers performed slightly better than noncarriers on the auditory verbal learning test, short-term recall, long-term recall, and percent recall. By the end of the study period, carriers had declined significantly more than noncarriers in short-term recall as well as in mental arithmetic, digit symbol substitution, and freedom from distractibility—all frontal mediated cognitive domains.

—Michele G. Sullivan