Novel Alzheimer's Drug Falls Short at Phase III

BY MICHELE G. SULLIVAN

Another potential Alzheimer's disease drug failed after Eli Lilly & Co. pulled the plug last month on its phase III study of semagacestat, a gamma secretase inhibitor designed to reduce the aggregation of beta-amyloid into brain plaques.

This latest in a string of Alzheimer's drug flops carried an especially harsh sting, said Dr. Marwan Sabbagh, an investigator in the IDENTITY (Interrupting Alzheimer's Dementia by Evaluating Treatment of Amyloid Pathology) and IDENTITY-2 trials.

"Unlike some of the previous failed phase III studies, IDENTITY was a well-designed, well-powered study of a drug with a very specific mechanism," he said in an interview.

The company announced its decision after a planned interim analysis of both trials showed that patients who took the study drug did not experience cognitive improvement and, in fact, showed a significant worsening of cognition and the ability to perform activities of daily living, compared with those taking placebo. In a press statement, the company also noted that semagacestat was associated with an increased risk of skin cancer. No data were available as to the risk ratio, crude incidence rate, or type of cancers observed.

IDENTITY and IDENTITY-2 randomized more than 2,600 patients with mild to moderate Alzheimer's disease to either placebo or 140-mg semagacestat for 24 months. Although the trials have been halted, Lilly will continue to follow patients and analyze safety and efficacy data from both studies for at least another 6 months.

Dr. Sabbagh of the Banner Sun Health Research Institute in Sun City, Ariz., said it is still too early to understand why those who took the drug fared worse than the placebo group, or how it may have affected skin cancer risk.

'My fear is that a drug will be shelved when in fact it might be a good choice in a presymptomatic scenario.'

DR. SABBAGH

Semagacestat made an unusual leap from phase II to phase III, Dr. Sabbagh said. "It was a very different approach. Their phase II study met the safety end points, but did not look at [cognitive] efficacy." Instead, he said, Lilly moved the drug forward on the basis of significantly reduced beta-amyloid levels in blood plasma. The drug does not decrease the existing Alzheimer's plaque burden. Instead, its aim is to prevent new plaques. It decreases the amount of plaque-forming beta-amyloid protein by changing the point at which gamma secretase cleaves the amyloid precursor protein. The resulting shorter peptide lengths do not aggregate into brain plaques like those with 40 and 42 amino acids—amyloid beta40 (Abeta40), and Abeta42.

VITALS

Major Finding: Alzheimer's patients taking semagacestat fared worse than placebo patients, both in cognition and function.

Data Source: A phase III study of more than 2,600 patients who took semagacestat 140 mg daily.

Disclosures: Eli Lilly & Co. sponsored the studies. Dr. Sabbagh reported no financial ties with the company.

In the phase II study, patients who took 100 mg semagacestat daily had a 58% reduction of Abeta40 in the plasma; those who took 140 mg daily had a 65% reduction. However, there were no significant reductions in CSF Abeta40 levels (Arch. Neurol. 2008;65:1031-8).

Although the drug was generally well tolerated, the phase II researchers, led by Dr. Adam Fleischer of University of California, San Diego, expressed some concern about safety. All gamma secretase inhibitors interfere with Notch signaling. The Notch protein is important in programmed cell death; blocking it particularly affects organ systems with high cell turnover, such as the gut and immune system. In the phase II trial, there were more—but not significantly more—gastrointestinal side effects in the active group (27% vs. 13%).

Although the drug mobilized Abeta40 in phase II, the changes did not translate into clinical benefit during phase III, Dr. Sabbagh said. But that finding may mean that semagacestat's failure is a case of poor timing rather than poor efficacy.

"By the time you have Alzheimer's symptoms, you already have a critical mass of amyloid plaque, and this stays relatively constant as you progress through the disease," he said.

"The question is, will any antiamyloid drug have a meaningful effect if it's given after the plaques have already developed?"

It may be time, he said, to think of Alzheimer's as a biphasic disorder. "Maybe our amyloid-based therapies should be used in the presymptomatic phase, before the plaques build to that critical level. Other drugs might be more useful in the symptomatic stage."

Dr. Sabbagh said he wondered if some of the Alzheimer's drugs that have been abandoned after failing their phase III studies might be more successful if used earlier in the disease course.

"My fear is that a drug will be shelved when in fact it might be a good choice in a presymptomatic scenario, when amyloid plaques are just beginning to develop."

With the enormous leaps now being made in amyloid imaging, researchers are pushing back the diagnostic timeline, identifying patients at the very onset of mild cognitive impairment—and perhaps even before any memory complaints appear.

"A drug like semagacestat would be interesting to study in patients at that stage. Don't chuck the product altogether; back it up into an earlier phase and see if the results are any different." ■

Plasma Beta-Amyloid Fluctuations Signal Cognitive Decline

BY MARY ANN MOON

FROM ARCHIVES OF NEUROLOGY

When plasma levels of beta-amyloid rise above normal and then decrease or stabilize in healthy elderly patients, it signals the onset of a rapid decline in several cognitive domains, a study has shown.

In most patients, that decline takes the form of Alzheimer's disease. In the minority who don't develop full-blown dementia, there is a marked cognitive decline that primarily affects memory rather than language or visuospatial domains, said Stephanie A. Cosentino, Ph.D., of the Taub Institute for Research in Alzheimer's Disease and the Aging Brain, New York, and her associates.

Studies have shown a correlation between elevated plasma beta-amyloid (Abeta) levels and the development of mild amnestic cognitive impairment or frank Alzheimer's disease (AD) within a few years. But other studies have found that decreasing, rather than elevated levels, correlate with these cognitive declines.

Dr. Cosentino's study suggests that the timing of the plasma sampling and of the subjects' disease stage may account for these discrepant results.

The investigators used data from a population-based study of aging to examine the link between plasma levels of the soluble oligomers Abeta-40 and -42 and cognitive changes. A total of 880 nondemented study subjects provided one blood sample at baseline in 1999 and a second sample 4.5 years later. They underwent a battery of neuropsychological tests at 18-month intervals.

During follow-up, 481 remained cognitively healthy, 329 developed cognitive or functional impairment but no dementia, and 70 developed AD. The cohort involved nearly equal percentages of Hispanics (37%), whites (31%), and African Americans (31%).

"Overall, high initial levels of plasma Abeta-40 and Abeta-42, and stable or decreasing Abeta-42 at follow-up, were associated with faster global cognitive decline regardless of dementia status," Dr. Cosentino and her associates wrote (Arch. Neurol. 2010 Aug. 9 [doi:10.1001/archneurol.2010.189]).

Subjects whose initial Abeta-40 and Abeta-42 levels were in the top three quartiles had significantly faster cognitive decline than did those in the lowest quartile. Those with either decreasing or stable Abeta-42 levels at the second measurement had significantly faster cognitive decline than other subjects.

An elevated level of Abeta-42 at baseline predicted cognitive decline in memory, language, and visuospatial domains, with subjects in the highest quartile of beta-amyloid level consistently declining significantly faster than subjects in the lowest quartile. However, in the subgroup of subjects who remained cognitively unimpaired, those with high baseline levels of Abeta-42 showed declines only in the memory domain.

The researchers suggested that these subjects may be in the early stages of AD but have not yet shown sufficient decline in nonmemory domains to meet the criteria for dementia. Alternatively, they may remain free of dementia due to biological factors such as the ability to clear high levels of beta-amyloid or psychosocial factors such as the presence of cognitive reserve.

VITALS

Major Finding: High initial levels of plasma Abeta-40 and Abeta-42, and stable or decreasing Abeta-42 at follow-up, were associated with faster global cognitive decline regardless of dementia status.

Data Source: Plasma samples and neuropsychological tests from 880 participants in a prospective, population-based study of aging and dementia in northern Manhattan.

Disclosures: The study was funded by grants from the National Institutes of Health. The investigators had no relevant disclosures to report.

"Another interpretation of the association between plasma Abeta-42 and memory is that amyloid changes are an important factor in cognitive aging, independent of underlying AD. Stated differently, the observable change in both plasma Abeta and memory in this group could be a fundamentally different process than that involved in AD or might fall short of a critical threshold beyond which the full pathological presentation and clinical dementia syndrome of AD would unfold," they wrote.

Future studies must "determine more definitively the specificity of Abeta profiles for predicting dementia vs their significance for cognitive aging more generally," they added.

The study was funded by the National Institutes of Health. The researchers had no conflicts to report. ■